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THE FUNCTIONS AND INTEGRATION OF THE INTERCOSTAL MUSCLES¹

C F HOOVER

CLEVELAND

The study of intercostal muscle function began with Galen, who believed the external intercostals to be expiratory and the internal intercostals inspiratory. This teaching was unquestioned until Vesalius, thirteen hundred years later, interpreted both external and internal muscles as having the same function. Thomas Willis, of Oxford, in 1673 for the first time interpreted the external muscles as inspiratory and the internal as purely expiratory. In 1748, Hamberger devised his famous model and the theory which has been quoted in all subsequent physiologic literature on respiration. Luciani says Hamberger's model "is an incomplete reproduction of costal excursion, but it served to elucidate the mechanism"—faint praise but quite sufficient for a scheme which misrepresents both costal excursion and intercostal function.

The only experimental confirmation of Hamberger's theory that is at all worthy of the problem is Martin and Hartwell's, an account of which was published in 1879. These experimenters isolated a pair of ribs by cutting all the intercostal structures which bound them above and below and with the sternum, but left intact the blood and nerve supply to the space between the two experimental ribs. The external intercostal muscle uniting the two ribs was then severed through its entire extent, and finally both ribs were cut so as to leave two segments of the ribs connected only by the internal intercostal muscles, the blood and nerve supply of which were left intact. Artificial respiration was employed and then, when automatic respiratory movements were set up after artificial respiration was suspended, the internal intercostal muscle was observed to contract during expiration only.

So far as this observation goes it is satisfactory, but it does not prove that the external intercostals are never expiratory, nor does it prove that the internal intercostals are never inspiratory. In this

* Read before the Experimental Section of the Cleveland Academy of Medicine November, 1921

experiment also no account is taken of the varying respiratory responses consequent on resistance to entrance and exit of air or varying amounts of the minute volume of air. Martin and Hartwell also failed to consider the varying effects on respiratory movements produced by different degrees and kinds of anesthesia and varying degrees of exhaustion of the respiratory innervation. Nor did these experimenters consider the integration of all the respiratory muscles in a normal animal.

With these considerations in mind, my experimental work has led me to formulate the following theses:

1 With tranquil respiration, only the external intercostals are activated during inspiration, and in expiration neither external nor internal intercostal muscle is employed.

2 With great hyperpnea, the external intercostals are activated during inspiration, and in expiration the internal intercostals only may be activated, but when the abdominal muscles are brought into use, either because of resistance to the exit of air or by intense hyperpnea, then the external muscles are synergically employed with the abdominal muscles. The external muscles are employed in expiration only when the abdominal muscles are requisitioned.

3 The internal intercostal muscles are employed in inspiration only when in the presence of hyperpnea there is added a resistance to the entrance of air.

4 The normal inspiratory and expiratory excursions of the ribs are determined not by the alternating actions of the two sets of intercostal muscles but by their integration with muscles that convert the results of their action into either an inspiratory or an expiratory effect. These auxiliary muscles are the scaleni and serratus posticus superior for inspiration, and the triangularis sterni and serratus posticus inferior for expiration.

Briefly stated, the external intercostal muscles are employed in inspiration in all respiratory conditions. There is a high threshold for their use in expiration, and this is passed only when they are activated synergically with the abdominal muscles. The internal are employed in expiration in hyperpnea, and have a threshold for expiratory use that is lower than that for the external intercostals. The internal intercostals are required in inspiration only in the combined presence of hyperpnea with resistance to the entrance of air. The highest threshold is for the inspiratory employment of the internal intercostal muscles, and then in descending order come the external intercostals in expiration, the internal intercostals in expiration, and finally the external muscles in inspiration.

PARALYSIS OF THE INTERCOSTAL MUSCLES—The best example of the functional loss of the intercostal muscles that it has been my fortune to see was in a man about 50 years of age, who had had a severe attack of poliomyelitis when 25 years old. This man was in good health and suffered only the disability which resulted from poliomyelitis. He had a widely distributed and severe paresis and atrophy of the thoracoscapular and upper extremity muscles of both sides, and there was involvement of the muscles of the pelvic girth and both thighs and both legs. There was nowhere any evidence of sensory paresis. He had sufficient use of his arms and legs so that he was able to go about, though with considerable difficulty, and was able to take care of himself. Of the muscles employed in respiration, only the intercostals, triangularis sterni and serrati postici, superior and inferior, were involved, the scaleni, diaphragm and abdominal muscles being intact. All of the intercostal muscles were completely paralyzed with the exception of those going to the ninth, tenth, eleventh, and twelfth ribs of the right side. These four bottom ribs of the right side were the only ones that moved in response to intercostal muscles. That part of the right costal border formed by the ninth, ten, eleventh and twelfth ribs moved laterad in inspiration, and those ribs had also a normal bucket-handle movement. In inspiration the remaining portion of the right costal margin and the entire left costal margin moved toward the median line.

Estimated by his height and weight, his lungs should have had a vital capacity of 3,800 c c, and without the aid of his intercostal muscles he did have a vital capacity of 3,200 c c. This capacity was quite sufficient for respiratory purposes, but he could not expel an explosively from his lungs as required by a cough or sneeze. He had all the incentive to sneeze and completed the reflex procedure, but his sneeze was ineffective on account of the want of explosive expulsion of air. He had also observed that it was difficult for him to expel hard fecal matter. He said that a few years after his recovery from poliomyelitis he had an attack of bronchitis, which gave him much distress on account of his inability to expel mucus from his trachea, but he instinctively discovered that he could cough with considerable success if he placed his arms about his thorax and then threw himself on his side against the mattress of the bed. The man seemed to cough into instead of out of the lung. He could approximate his vocal cords with normal vigor, and the abdominal muscles were vigorous, from the strength of his laryngeal and abdominal muscles the observer would expect a vigorous cough, but he was unable to produce it. When the sides of his thorax were firmly supported by the hands of an attendant, he was able to cough like a normal person.

The ability to compress his lungs was tested by having him blow into a mercury manometer. In carrying out this test, in order to make sure that the patient did not employ his buccal muscles to raise the pressure in the manometer, he was required to blow through a tube in one nostril. He could raise the pressure just 50 mm, but with normal expiratory muscles he could have raised it 100 mm. It was quite apparent that the deficient compression of his lungs was due to paralysis of his intercostal muscles, which deprived him of circumferential constriction of the thorax.

The part played by the intercostal muscles in inspiring against resistance was shown when the patient was instructed at the end of a forced expiration to inspire with all his might through a tube (connected with a mercury manometer), which was inserted in a nostril while the mouth and other nostril were held shut. The highest column of mercury he could raise in this manner was 46 mm. In view of the fact that a normal person can inspire against a resistance that is 90 per cent as great as the positive pressure he can raise within the lung, it is apparent that the loss in forceful inspiratory action was proportionately the same as the loss in power of compressing the lungs.

If we consider the pneumatics of the experiment, the basic reasons for his disability stand out with great clearness. There were at least 1,000 cc of residual air in his lung at the end of a forced expiration, and then he added 3,200 cc by the use of his diaphragm and scaleni. While this volume of air was contained in the lung, he blew into the manometer by contracting his abdominal muscles, which served to drive the diaphragm upward. By this effort the mercury manometer registered a pressure of 50 mm, therefore, his lungs were compressed to $\frac{750}{800} \times 4200$, which equals 3,937 cc. The diminution in volume of the 4200 cc under a pressure of 50 mm of mercury equaled 263 cc.

In this formula $750 =$ the barometric pressure which prevailed at the time,

$800 =$ pressure to which the contained air in the lung was subjected by the muscular effort

If, as a normal man should, he had been able to attain an intrapulmonic pressure of 100 mm mercury, the 4,200 cc of air would have been compressed to a volume of 3,705. There would therefore, have been a further diminution in volume of 222 cc for the rise in pressure from 50 to 100 mm mercury. From the original estimate of this man's vital capacity, we assume that he was deprived of only 600 cc by paralysis of his intercostal muscles. Now, suppose in the act of blowing into the manometer he had been able to accomplish a completely normal expiratory excursion of his ribs, he would have further reduced the volume of air in his lungs by 600 cc. Had his

intercostal muscles been sufficiently strong to accomplish this compression, he would have raised the pressure in the manometer to 193 mm mercury—that is, 143 mm higher than the 50 mm he was able to attain. This is estimated according to the following formula

$$\frac{750}{800 + x} \times 4,200 = 3,337$$

In this formula, 750 = barometric pressure

800 = mm of mercury pressure which was actually produced by the patient's muscular effort

x = the unknown added pressure (143 mm mercury which would have been necessary to compress the air 600 cc less than the volume which was attained by the effort he actually employed. As shown above, this volume was 3,937)

4,200 = the original volume of air in the lung at prevailing barometric pressure

This computation shows in an interesting way the physical basis for the man's disability to constrict his thorax for want of his intercostal muscles. He was able to raise his intrapulmonic pressure just half as high as if he possessed normally functioning intercostal muscles, but the vital capacity of his lungs was impaired only 15 per cent of the normally expected amount.

The power of lowering air pressure in the lungs by inspiratory effort was also diminished in the same proportion as was the power of compression. The losses in power of circumferential constriction and of expansion were the same, which indicates that exactly the same musculature is employed in both, or at least that an equal loss for both processes is incurred by motor paralysis of all the intercostal muscles. Therefore, if it can be shown that both external and internal intercostals are employed in forced compression, the corollary follows that both sets of muscles are employed in forced expansion.

Loss of all intercostal function, as shown by the preceding discussion, leaves the patient in respiratory comfort with the loss of only between 15 and 20 per cent of vital capacity. The major disability incurred by paralysis of all the intercostal muscles lies wholly within any effort that demands compression or distension of the lung against resistance.

The opportunity to examine the thoracic excursion of a man with normal cardiorespiratory function, with the exception of motor paralysis of the intercostal muscles, was a rare opportunity. I can find no other similar case in medical literature. The surprising

features of his disability were the slight loss of vital capacity and the great loss in the ability forcibly to compress and to distend the lungs. It is obvious that the slightness of the diminution in vital capacity was not due so much to the normally small share of the lost costal excursion in lung distension as to the abdominal muscles—which by their attachments to the entire costal borders and lower end of the sternum were able to pull the lower six pairs of ribs downward and toward the median line and to pull the sternum with its attached ribs in a downward direction—and also to the inspiratory aid of the scaleni, which will be considered later in the discussion.

CONTRIBUTION OF EACH GROUP TO VITAL CAPACITY—In this relation it seemed desirable to learn about how much of the vital capacity may be lost when both the intercostal and abdominal muscles are paralyzed. Under such conditions the actual share of phrenic excursion in procuring vital capacity can be estimated, because in expiration the ribs cannot be drawn into a forced expiratory position by the abdominal muscles.

EXPERIMENT 1—A vigorous dog, weighing 11 kilos, was used. Before the administration of ether there was given only $\frac{1}{4}$ grain morphin so that the respiratory center would be depressed as little as the operative conditions would allow. A tracheal cannula was inserted and connected with the reservoir of a Benedict apparatus that contained 75 per cent oxygen and 25 per cent carbon dioxide. This was done with the idea that if the animal were under light anesthesia he would exhibit nearly his whole vital capacity in the ensuing hyperpnea that would be demanded by rebreathing such a high percentage of carbon dioxide. As will be later shown it was closely approximated.

In Figure 1, line A, is seen the tracing made on a drum revolving at the rate of 5 mm per second. The time marker is in one-fifth second. The dog rebreathed into a Benedict apparatus with a clamp on the tubes leading to the canister. The largest excursion of the reservoir recorded a tidal air of 704 cc. The spinal cord was then sectioned at the level of the top of the body of the first dorsal vertebra. The scaleni and diaphragm were the only respiratory muscles left intact, the intercostals, triangularis sterni, serrati postici and abdominal muscles being paralyzed. During inspiration the diaphragm had a large excursion, as shown by the inspiratory protrusions of the upper abdomen, both costal margins were drawn toward the median line and the lateral aspects of the thorax were slightly retracted. The tracheal cannula was reconnected with the Benedict reservoir within a few minutes after the spinal cord was sectioned. The tracing in line B, Figure 1, was then made on a drum slowly revolving at a rate of 1 mm per second. The transitions from inspiration to expiration and vice versa are seen to be at first very prompt and then gradually there developed a change in the automatic steering. The transition from expiration to inspiration remained the same, but there was a prolongation of the time between the end of inspiration and the end of expiration.

As seen in Figure 1, line A at X before the cord was sectioned the duration of an inspiration was four-fifths second and of an expiration seven-fifths second. Lines C, D, E and F (Fig 1) are tracings of the respiration after the cord was sectioned. The speed of the drum was 5 mm per second, and the time marker registered in one-fifths of a second. At Y, line E, the duration of an inspiration was four-fifths second, but from the height of inspiration to the end of expiration was thirteen-fifths second. The diaphragm was held near the maximum point of excursion for nine-fifths second, and then it was

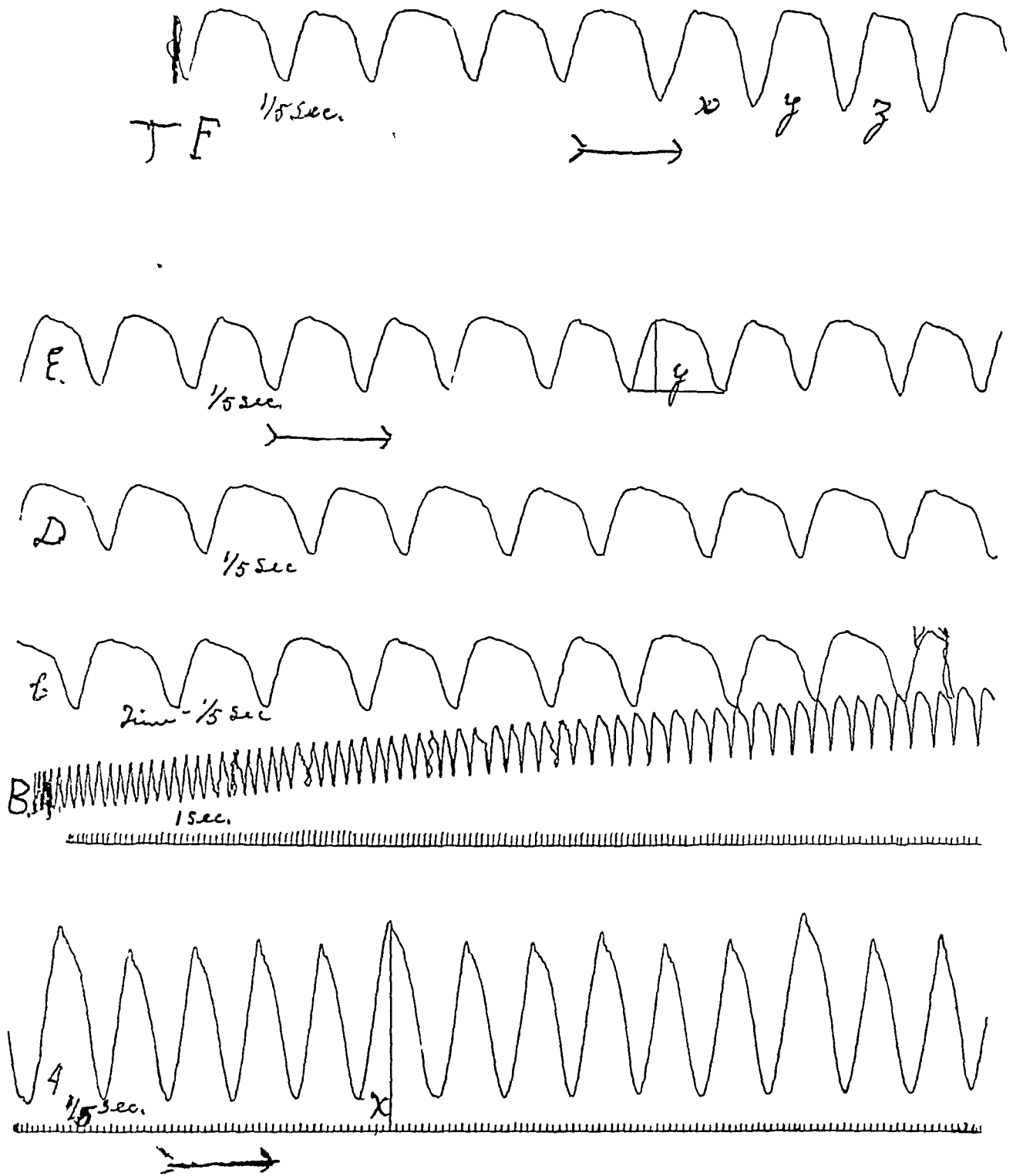


Figure 1

relaxed as the retractile lung expelled its contents in the remaining four-fifths second. After section of the cord the largest tidal air recorded was 308 cc which is only 43 per cent of the tidal air procured before the intercostal system and abdominal muscles were paralyzed. Under these conditions 67 per cent of the vital capacity was lost, whereas in the patient with paralyzed intercostals and intact abdominal muscles there was a loss of only 15 per cent of the vital capacity.

An attempt was made to simulate the forced expiratory phase of the patient with paralyzed intercostals and active abdominal muscles by compressing the dog's abdomen with the palms of both hands and at the same time pulling in both costal margins by the finger tips (Fig 1, line F at x, y, z). This procedure increased the tidal air from 308 to 440 cc, which is 62 per cent of the vital capacity under normal conditions. Of course this procedure did not adequately represent the function of normal abdominal muscles, but it indicates how the mechanism could be approximated. Cutting the cord slowed the respiratory rate from 24 to 16 per minute, but the slowing of the rate was due to the change in the automatic steering, which consisted in a delay of the transition from inspiration to expiration.

To determine (before the dog's cord was severed) how nearly the tidal air equaled the vital capacity, the pluck was removed and measurement was made of the volume of air that could be expressed from the lungs after they were given their maximum distension. This was found to be 1,012 cc. If from this we subtract 200 cc for residual air, there remain 812 cc, which is only 94 cc in excess of the tidal air (708 cc) obtained when the animal was breathing the high percentage of carbon dioxide. When we consider the possible excess of distension obtained by blowing up the excised lungs above the maximum inspiratory distension during life, it is apparent that the 704 cc of tidal air closely approximated the dog's vital capacity when all the respiratory muscles were intact, and 308 cc the vital capacity after the intercostal system and abdominal muscles were paralyzed.

During the time the dog was breathing his maximum minute volume of air when the cord was intact, the abdominal muscles were vigorously contracted during expiration, and although the intrapleural pressure was not measured during that time, the fact that the abdominal muscles were vigorously contracted is good evidence that the pressure in the pleural cavity was raised above barometric pressure. The active vigor with which expiration is performed in such experiments depends on the depth of anesthesia and the state of exhaustion of the animal. When the intercostals alone are paralyzed, the abdominal muscles contribute to the vital capacity by their expiratory aid, as shown in the patient whose intercostals were paralyzed while the abdominal muscles were intact.

Experiment 2 was done to show how much of the vital capacity of an animal is sacrificed when the diaphragm is paralyzed and the scaleni, intercostals and abdominal muscles are intact.

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To determine (before the dog's cord was severed) how nearly the tidal air equaled the vital capacity, the pluck was removed and measurement was made of the volume of air that could be expressed from the lungs after they were given their maximum distension. This was found to be 1,012 c.c. If from this we subtract 200 c.c. for residual air, there remain 812 c.c., which is only 94 c.c. in excess of the tidal air (708 c.c.) obtained when the animal was breathing the high percentage of carbon dioxide. When we consider the possible excess of distension obtained by blowing up the excised lungs above the maximum inspiratory distension during life, it is apparent that the 704 c.c. of tidal air closely approximated the dog's vital capacity when all the respiratory muscles were intact, and 308 c.c. the vital capacity after the intercostal system and abdominal muscles were paralyzed.

During the time the dog was breathing his maximum minute volume of air when the cord was intact, the abdominal muscles were vigorously contracted during expiration, and although the intrapleural pressure was not measured during that time, the fact that the abdominal muscles were vigorously contracted is good evidence that the pressure in the pleural cavity was raised above barometric pressure. The active vigor with which expiration is performed in such experiments depends on the depth of anesthesia and the state of exhaustion of the animal. When the intercostals alone are paralyzed, the abdominal muscles contribute to the vital capacity by their expiratory aid, as shown in the patient whose intercostals were paralyzed while the abdominal muscles were intact.

Experiment 2 was done to show how much of the vital capacity of an animal is sacrificed when the diaphragm is paralyzed and the scaleni, intercostals and abdominal muscles are intact.

EXPERIMENT 2—A dog weighing 17 kilos was given $\frac{1}{4}$ grain morphin prior to ether anesthesia. After insertion of a tracheal cannula, the animal rebreathed into the Benedict reservoir containing 75 per cent oxygen and 25 per cent carbon dioxid. During this period of intense hyperpnea, the dog very vigorously contracted the abdominal muscles during expiration, so that we have good reason for saying he was employing his maximum expiratory and inspiratory efforts. The largest tidal air was 836 c c. The phrenic nerves were then sectioned in the lower portion of the cervical region and rebreathing of a high percentage of carbon dioxid was resumed. During this period the outward movement of the costal margins was very greatly exaggerated, and in expiration the abdominal muscles were strongly contracted. The largest tidal air procured was 418 c c.

An incision was then made in the abdomen and the leaves of the diaphragm were inspected. They were found to be paralyzed on both sides, but there was a vigorous contraction of the crura of the diaphragm, which evidently received some nerve supply from the cord below the origin of the phrenics. The active contraction of the crura drew the mid-portions of the diaphragm slightly downward and backward, and no doubt contributed somewhat to stabilizing the whole diaphragm, so that it did not ascend during inspiration when the intercostals were strongly activated.

The inability to get absolute paralysis of the entire diaphragm by sectioning the phrenic nerves makes the estimation of the diaphragm's contribution to vital capacity somewhat doubtful. The manner in which this dog's diaphragm behaved will not allow the assumption that all the share of the diaphragm in inspiration was eliminated. However, so far as our observations go, they indicate that paralysis of the intercostal muscles with preservation of the abdominal muscles reduces the vital capacity only about 15 per cent, whereas paralysis of the diaphragm which follows sectioning of the phrenic trunks reduces the vital capacity about 50 per cent.

To see how nearly the maximum tidal air of the animal represented his vital capacity, the intercostal spaces on both sides were freely opened and after the animal died the lungs were blown up to their maximum capacity in situ within the thorax, and then the escaping air was measured as the lungs passively contracted. The amount of air thus expelled from maximum distension to maximum contraction was 1,276 c c. So it seems that 836 c c closely approximates the animal's vital capacity when we consider the residual air to have been about 300 c c.

This experiment was done on three different animals. In one experiment there was very slight action of the pillars of the diaphragm after the phrenics were cut. In two animals that part of the diaphragm inserted on the vertebrae contracted with great vigor, but in all the animals that part of the diaphragm inserted laterally to the vertebrae and on the costal borders was completely paralyzed. This observation was confirmed by making an incision through the diaphragm so that the entire extent of the phrenic structure could be palpated between the thumb and fingers.

Experiment 3 was employed to give some conception of the ventilatory capacity of the intercostals when the diaphragm was paralyzed and the abdominal muscles eliminated by cutting away their attachments to the costal borders

EXPERIMENT 3—After a preliminary dose of $\frac{1}{4}$ grain morphin, a tracheotomy tube was introduced into the trachea of a dog under ether anesthesia and connected with a Benedict reservoir containing 20 per cent carbon dioxide and 80 per cent oxygen. The time recorded is in one-fifths of a second. The

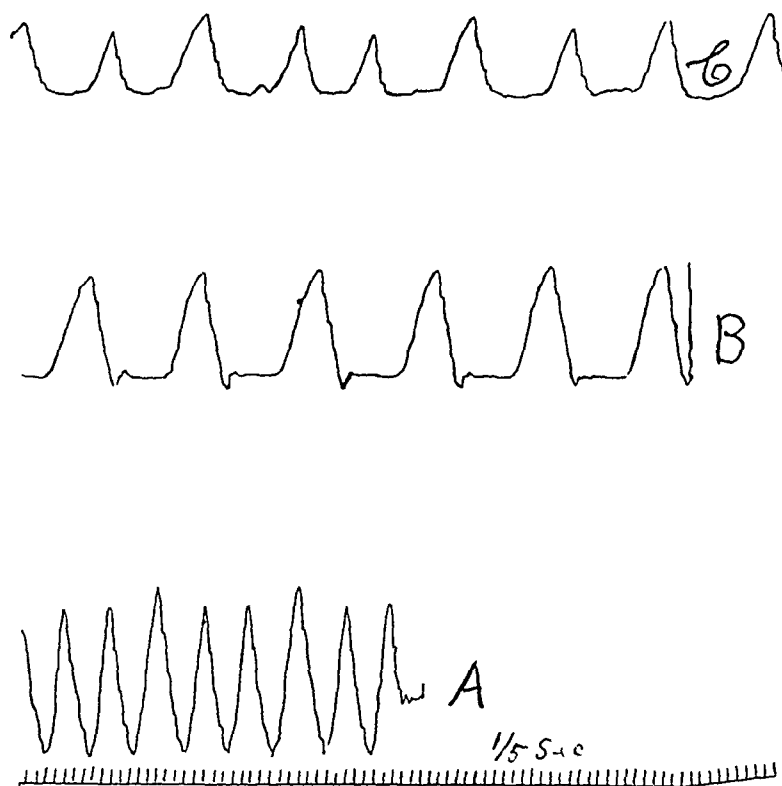


Figure 2

lower line A, Figure 2 records the respiratory excursion while the dog was rebreathing this high percentage of carbon dioxide. The largest tidal air recorded was 484 cc. Both phrenic nerves were then sectioned in the lower cervical region and the respiration recorded on line B. The largest tidal air recorded was 330 cc.

The linea alba was then incised up to the diaphragm and all the attachments of the abdominal muscles to the costal borders and last rib were severed. Tracing C was then made and the largest tidal air was 220 cc.

CONFORMATION OF THE THORAX AND MANNER OF COSTAL EXCURSION

Before entering on a discussion of muscular function, the next problem to consider is the conformation and excursion of the thoracic cage. The bony cage of the thorax consists of two parts, whose mechanisms of respiratory excursion differ in several details. The

upper portion, or cuirass, consists of the sternum and upper five ribs, which unite transversely with the sternum at nearly right angles. In inspiration the anterior transverse portions of the second to the fifth ribs (inclusive) are rotated in a vertical plane which intersects the rib at its midclavicular line and the articulation between the head of the rib and the transverse process of the vertebrae. The lateral parts of these ribs rotate in a vertical plane which intersects the rib in its midaxillary line and the middle of the median plane of the thorax. Both of these radii of rotation for these four ribs increase in length from above downward as their arches increase in size.

In the Hamberger model, which supposedly represents the elevation of the ribs, the radii of rotation for rib segments are wrongly employed to represent the ribs, and therefore, show a widening of the distance

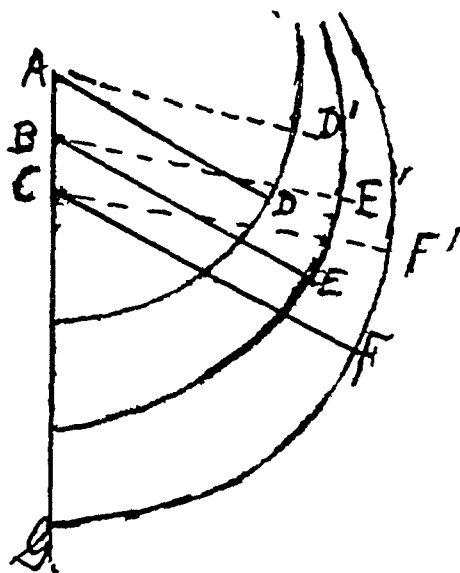


Figure 3

between these supposed structures as they move upward in parallel relation. The widening is true for the radii of rotation of rib segments but not for the intercostal spaces, which should be measured by the distance between the ends of the radii. This will be seen in Figure 3.

In the above diagram let A-G be the vertebral column and A-D, B-E and C-F the radii of rotation of the anterior parts of three ribs. As the radii move upward or in a cephalad direction, retaining the parallel relation so that they are brought into the positions of A-D', B-E' and C-F', the distances between the parallel radii increase but the distances between the ends of the radii diminish, and it is the distance between the ends of the radii which should represent the breadth of an intercostal space. An apparatus was designed to illustrate this point (Fig. 4).

In Figure 4, A, the large perpendicular piece represents the side of the vertebrae. The three parallel structures at bent angles with the

vertebrae represent the radii on which segments of the arches of the upper ribs rotate. The three transverse pieces attached to the ends of the radii represent segments of the arches of the ribs, and the three rubber bands which connect the segments of the ribs represent the intercostal muscles.

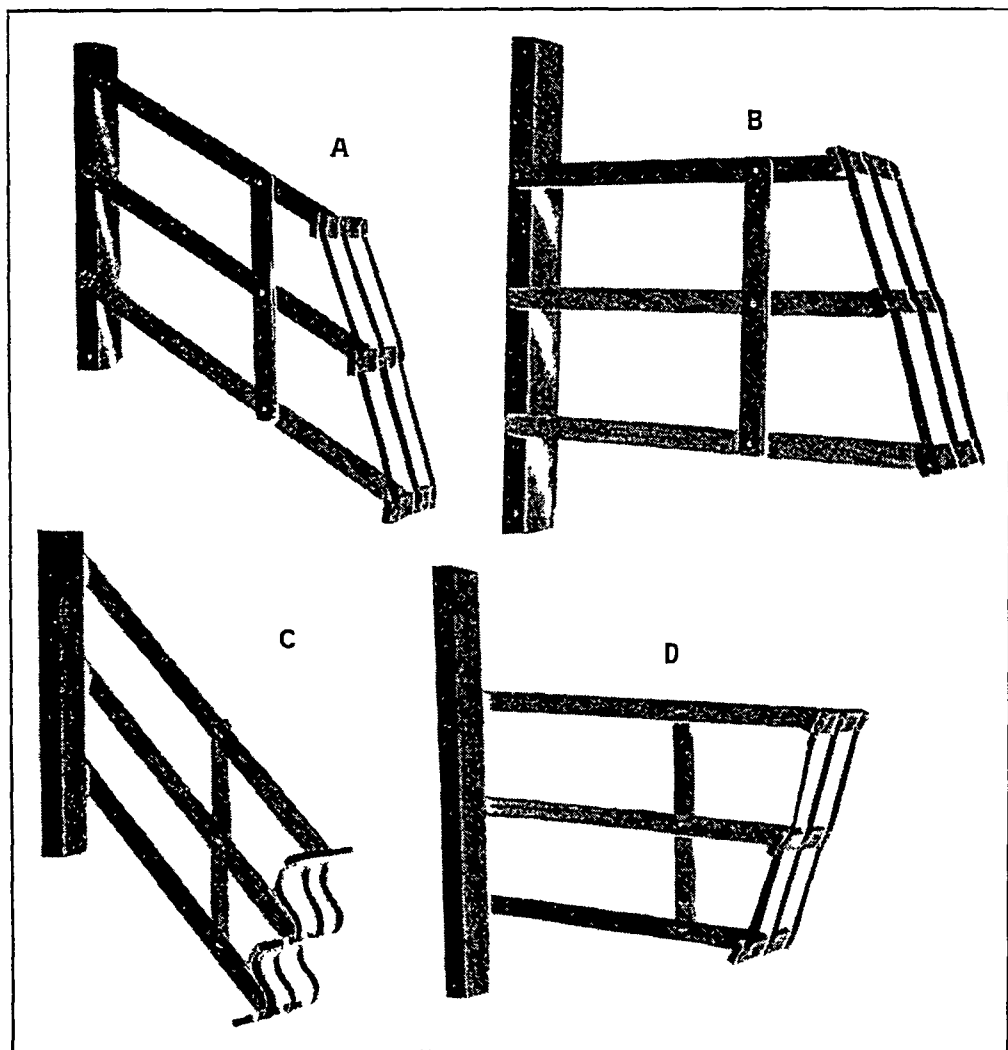


Figure 4

In B, as the three radii are released they rise to a right angle position on the vertebrae. The distances between the radii are enlarged, but the elastic bands which represent the intercostal muscles are shortened.

If the apparatus is turned upside down, we then have an illustration of the ribs at the base of the thorax where the arches of the ribs diminish in size as we descend.

In C, the three arms forming acute angles with the perpendicular median plane of the thorax represent the radii of rotation of the ninth,

tenth and eleventh ribs When the radii form an acute angle with the perpendicular, the bands representing the intercostal muscles are relaxed, and then if the radii are lifted into the horizontal position, as in D, the intercostal bands become taut This is just the opposite of the conditions which obtain in the upper thorax, where elevation of pairs of ribs in parallel relation narrows the intercostal spaces throughout their entire extent In the middle of the thorax, where the succeeding lower rib has the same sized arch, or in the lower thorax, where the succeeding lower rib has a lesser arch, elevation of ribs in pairs would widen the intercostal spaces but for provisions in the structures of the anterior extremities of the last seven ribs From the sixth to the tenth rib, inclusive, the angulation of the cartilaginous parts of the ribs with their bony parts permits an enlargement of the costochondral angle as the rib is elevated, and thus the entire arch of the rib is enlarged as it is drawn upward and outward by the intercostal muscles The straightening of the costochondral angle thus permits all that part of the rib which is lateral to the chondral portion to be rotated outward in a horizontal plane on a vertebral axis The capacity for outward rotation on a vertebral axis increases from the sixth to the twelfth ribs, inclusive, and is particularly ample in the floating ribs If these last seven ribs move upward in response to activation of the intercostal muscles attached to their upper borders, they must swing laterad, and thus, by increasing the length of the radii of cephalad rotation of their arches, the intercostal spaces retain a constant breadth This introduction of an additional axis of rotation for the lower seven ribs compensates for the widening of their intercostal spaces that of necessity would result if the radii of rotation of their arches were not enlarged as they are elevated during inspiration

It is an absurdity to suppose that direct action of the intercostal muscles in any phase of quiet respiration could possibly widen the spaces between ribs The mechanism just described shows how elevation of the ribs increases the circumference of the thorax at every level without stretching the parietal pleura, and maintains a constant breadth of the intercostal spaces In fact, the function of the intercostal muscles during inspiration is to elevate the ribs without widening the intercostal spaces The visceral pleura glides over the parietal pleura only in pulmonary excursion between the position of apnea (i e., the end of passive expiration) and that of maximum inspiration, and within this range of thoracic excursion the parietal pleura is maintained as a smooth, taut membrane—a condition that is very essential for the smooth functioning of lung extension From the position of apnea to that of forced expiration, when the ribs are all pulled downward and the lower seven are rotated mediad on their vertebral axes by the action of all the intercostals and the abdominal

muscles, so that the surface of the parietal pleura may present a slightly corrugated surface, but within this range of thoracic excursion there is no gliding between the visceral and parietal pleurae

This exposition of costal excursion clearly shows how the intercostal spaces, from the second to the fifth, inclusive, may either retain their breadth or be slightly narrowed in the process of increasing the circumference of that part of the thorax which has the rigidity of a cuirass, and it also shows how, if the ribs be permitted to move cephalad during inspiration, the lower intercostal spaces, from the sixth to the eleventh, inclusive, must retain their width unchanged by an outward rotation of the ribs on a vertebral axis. If this outward movement of the lower ribs is not allowed, then the lower part of the thorax is rib-bound and loses its contribution to pulmonary excursion in inspiration.

It thus become apparent how flattening of the subcardial and lateral portions of the diaphragm will lessen the vital capacity of the lungs not only because some phrenic excursion is lost but also because flattening of any part of the diaphragm lessens the outward rotation of the costal ends to which it is attached. Depression of the diaphragm renders a patient, so to speak, both phrenic bound and costal bound in the lower thorax. In cardiac disease, where the enlarged heart flattens the subcardial diaphragm and causes inspiratory narrowing of the subcostal angle, we can see how the loss of outward rotation of the involved ribs will contribute to a loss in vital capacity of the lungs. So that cardiac decompensation contributes to lessening of lung capacity not only by lung rigidity from stasis in the pulmonary circulation, but also by costal rigidity due to a loss of outward rotation in the sixth to the ninth ribs, inclusive.

To show the absurdity of the supposed widening of the intercostal spaces on inspiration, one needs only to stretch a tape from the top of the second rib in the midclavicular line to the eleventh rib in the midaxillary line, and it is then seen that from the end of a normal expiration, or the position of apnea, to a maximum inspiration, the distance between these two points remains unchanged. If the tape is stretched from the middle of the clavicle to any point on the lower ribs, the distance between the two points is found to be lessened during quiet inspiration. In other words, all excepting the first rib move cephalad during a moderate inspiration. In a forced inspiration the scaleni elevate the first rib and with it the clavicle.

Excepting the first interspace, every part of all the intercostal spaces retains an unchanged breadth during tranquil inspiration, excepting those parts which lie between the costal cartilages as they form an angle with the course of their respective rib and turn in a cephalad direction to join the sternum. These interchondral spaces

are decidedly widened during inspiration, as can be clearly seen in the dog when the intercostal spaces are uncovered. However, in this area of interchondral spaces, a considerable volume of muscle intervenes between the spaces and the parietal pleura, viz., the triangularis sterni and the transverse abdominal muscles, so the alternate widening and narrowing of these spaces with respiratory movements do not modify the contour of that part of the parietal pleura that lies underneath.

This exposition of costal excursion is confirmed by a dog experiment which was designed to produce an exaggeration of the normal excursion of the ribs.

EXPERIMENT 4 — Under morphin, $\frac{1}{4}$ grain, and ether anesthesia, both phrenic nerves were severed in the lower cervical region, and all the attachments of the abdominal muscles were cut away from the costal margins, and the ribs exposed by skinning one side of the thorax. By this means all restraint to costal excursion by the diaphragm and abdominal muscles was

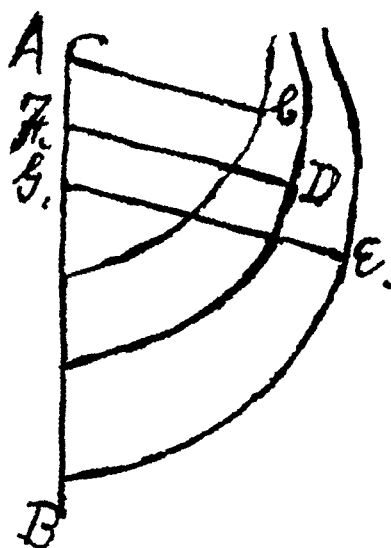


Figure 5

abolished. The dog was then made to rebreathe through a tracheal cannula connected with a Benedict reservoir that contained 25 per cent carbon dioxide and 75 per cent oxygen. The tube connecting the trachea with the reservoir was narrowed by means of a screw clamp so that inspiration and expiration were both much prolonged. It was thus possible to make a satisfactory inspection of the costal movements.

The second rib touched the first rib at the height of inspiration, and the second interspace was narrowed but not so much as the first. The narrowing of the interspaces during inspiration grew progressively less to the seventh, which retained an unchanged breadth during the entire respiratory cycle, but from the seventh space down to the twelfth, inclusive, there was a perceptible widening of the interspaces during inspiration and narrowing at the end of the forced expiratory effort. These observations were made on the intercostal spaces in a line drawn from the midclavicular line on the second rib to the midaxillary line on the thirteenth rib. It was clearly perceived that the interspaces in the upper half of the thorax, or cuirass, were narrowed in inspiration and widened in expiration, but in the lower half the interspaces were widened during inspiration and narrowed with expiration.

This strongly indicates that the intercostal muscles are concerned wholly with rotation of the ribs in laterad, cephalad and caudad directions, and have nothing to do with the breadth of the intercostal spaces. The varying breadth of the intercostal spaces is a mere incident in the process of enlarging the circumference of the thorax in all its levels during inspiration, and constricting the thorax circumferentially during expiratory efforts.

Figures 5 and 6 illustrate the rotations of the intercostal spaces in forced expiration.

In Figure 5 A-B represents a line drawn through the costovertebral articulation of three upper ribs. C, D and E are points on the first, second and third ribs in the mid-clavicular line. A-C, F-D, and G-E are the radii of

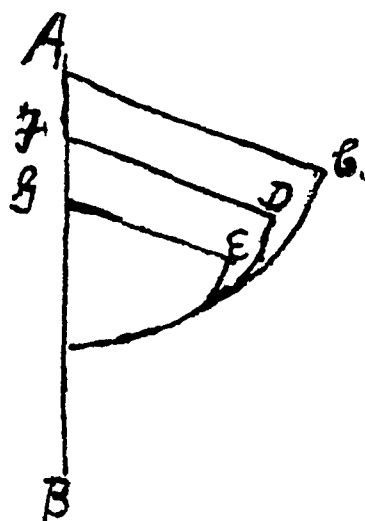


Figure 6

rotation of the points on the ribs. The distances between the arcs of rotation of these radii are seen to broaden as the arcs are drawn downward, which of course means that the intercostal spaces are slightly broadened in this part of the thorax as the ribs are pulled downward from the position of apnea to that of forced expiration. As we descend to the lower position of the thorax, there is a distinct narrowing of the intercostal spaces with forced expiration. This mechanism is described in Figure 6.

In Figure 6 let the line A-B represent a line on the middle of the vertical plane of the thorax, and C, D and E points on the ninth, tenth and eleventh ribs in the midaxillary line. A-C, F-D, and G-E are the radii of rotation of the points on the arches of these ribs, which diminish in size from above downward. As these ribs are drawn mediad and caudad the ends of the radii of rotation of neighboring costal segments, as shown by the arcs of excursion of the points C, D and E, will be approximated.

Thus, in thoracic excursion from the position of apnea to that of maximum expiratory compression, the upper part, or cuirass, and the lower or bellows part are both diminished in circumference, but in this process the upper intercostal spaces are slightly broadened and the lower intercostal spaces are narrowed.

COMPRESSION OF THE LUNGS BY INTERCOSTAL MUSCLES

As shown thus far by this study, the active part that the intercostal muscles may perform in compressing the lungs indicated the need of proving that the intercostals without the aid of the abdominal muscles can raise the pressure in the pleural cavity. The loss of one half the power of lung compression in our patient with paralyzed intercostals and intact abdominal muscles demanded proof that the intercostals without the aid of the abdominal muscles can compress the lungs.

Five animals were employed for this purpose. In four of them the abdominal muscles were eliminated by cutting all their attachments to the thoracic cage, and in one dog the dorsal cord was sectioned at the level of the fifth dorsal vertebra. The Meltzer pleural cannula and a tambour were used in each experiment to record the intrapleural pressure. The pleural cavity was injected with 100 c c of air to insure against occlusion of the intrapleural opening of the cannula, and after each tracing the contained air was aspirated by a graduated syringe to make sure there had been no leakage of air into the pleural cavity. The dog was made to rebreathe an atmosphere of 80 per cent oxygen and 20 per cent carbon dioxide against stenosis equal in inspiration and expiration and as great as the animal would tolerate—i e, the maximum resistance against which the dog would continue to breathe.

The rise in pleural pressure in expiration was always very moderate, only about one-quarter as great as the minus pressure obtained during inspiration. There was some doubt as to whether the moderate positive pressure attained in expiration was due to action of the intercostals or merely to pressure of the expanded thoracic cage passively resting on the lungs after they had been distended by torsion of the thorax and descent of the diaphragm during inspiration.

In several experiments only $\frac{1}{4}$ grain morphin was given before ether anesthesia was employed, and the animal was permitted to come sufficiently out of the ether anesthesia so that the conjunctival reflex returned. The idea was then conceived that the preliminary dose of morphin or the ether was responsible for the high threshold for active expiration, and therefore nitrous oxide anesthesia was employed without any preliminary dose of morphin. The results obtained by this method were very satisfactory.

EXPERIMENT 5—The dog with which the following tracings were made was a vigorous 2-year old terrier, weighing 12 kilos. The nitrous oxide anesthesia was begun by giving the anesthetic with a muzzle over the dog's nose while a tracheotomy was done, a tracheal cannula placed in position, and a Meltzer cannula inserted in the fourth intercostal space of the right side. An apparatus like that used in the surgical department of Lakeside Hospital was employed, and the anesthesia was administered by one of the anesthetists of the surgical service.

The original plan was to cut away all attachments of the abdominal muscles to the thoracic cage while the animal was under the anesthetic, and then with suspension of the nitrous oxid it was planned to give the dog a dose of apomorphin with the idea that during the vomiting effort that would follow, the action of the intercostals might produce a strong positive pressure in the pleural cavity. Quite beyond all expectation, while the dog's abdomen was still intact and without the introduction of any further resistance to expiration than was provided by the apparatus as usually employed in surgical work, the intrapleural tracing revealed a very strong positive pressure during expiration. After the tracing was finished, the pleural cavity was exhausted of air and only 100 cc could be withdrawn, the exact amount that was injected before the tracing was begun. It is, therefore, quite certain that pneumothorax was not a factor in the intrapleural pressure obtained.

In Figure 7, tracing A was made of the intrapleural pressure when the abdominal muscles were intact and there was no resistance offered to the entrance and exit of air beyond what the apparatus supplied. The time tracing is in seconds, and the horizontal line traces barometric pressure. The inspiratory or downward stroke is straight and the upward or expiratory stroke is equally so. As the tracing shows, each expiration was active and was attended by vigorous contraction of the abdominal walls. There was a free exchange of air between the lungs and the elastic bag that contained the mixture of nitrous oxid and oxygen. The intrapleural pressure, as determined by calibration of the tambour directly after the experiment, ranged between 80 and 130 mm of water above barometric pressure and between 60 and 80 mm of water below. The extent of intrapleural pressure does not indicate the volume of tidal air, because the intrapulmonic pressure was above the barometric. However, the excursions of the walls of the rubber bag showed the animal was freely exchanging air, and at the conclusion of the tracing, when the trachea was disconnected from the nitrous oxid apparatus, there was no hyperpnea.

This was a far better exhibition of active expiration under anesthesia than I had ever succeeded in procuring. It was therefore decided to cut away the attachments of the abdominal muscles from the thoracic cage and then see how the intrapulmonic pressure would behave with expiration under the influence of nitrous oxid.

Apomorphin was not given when the abdominal muscles had been cut, and the anesthetic was continued as before. Both inspiration and expiration were apparently conducted with much vigor. The whole surface of the diaphragm was plainly in view and could be seen to contract vigorously with inspiration. During expiration the under surface of the diaphragm pouched slightly caudad, and could be felt by the palpating hand to be under rather high pressure during the entire expiratory phase.

Tracing B, Figure 7, was then made of the intrapleural pressure. When this tracing was made, the only muscles that could possibly contribute to overcoming the intrapulmonic pressure were the intercostal muscles, the triangularis sterni, and some of the serratus posticus inferior. It seems certain that the intercostals must have been the dominant agent in compressing the lungs. The excursion of the thoracic cage was vigorous, and the costal borders were strongly moved lateral during inspiration.

At the right of the middle of the tracing the intrapulmonic pressure was nearly sufficient to distend the lungs, as shown by the fact that the intrapleural pressure during inspiration descended very little below the barometric line. That the dog was freely exchanging air was indicated by the thoracic excursion and the movements of the bag containing the anesthetic. At A the valve in the lateral opening of the tube connecting the tracheal cannula with the rubber bag was opened more freely to reduce the intrapulmonic

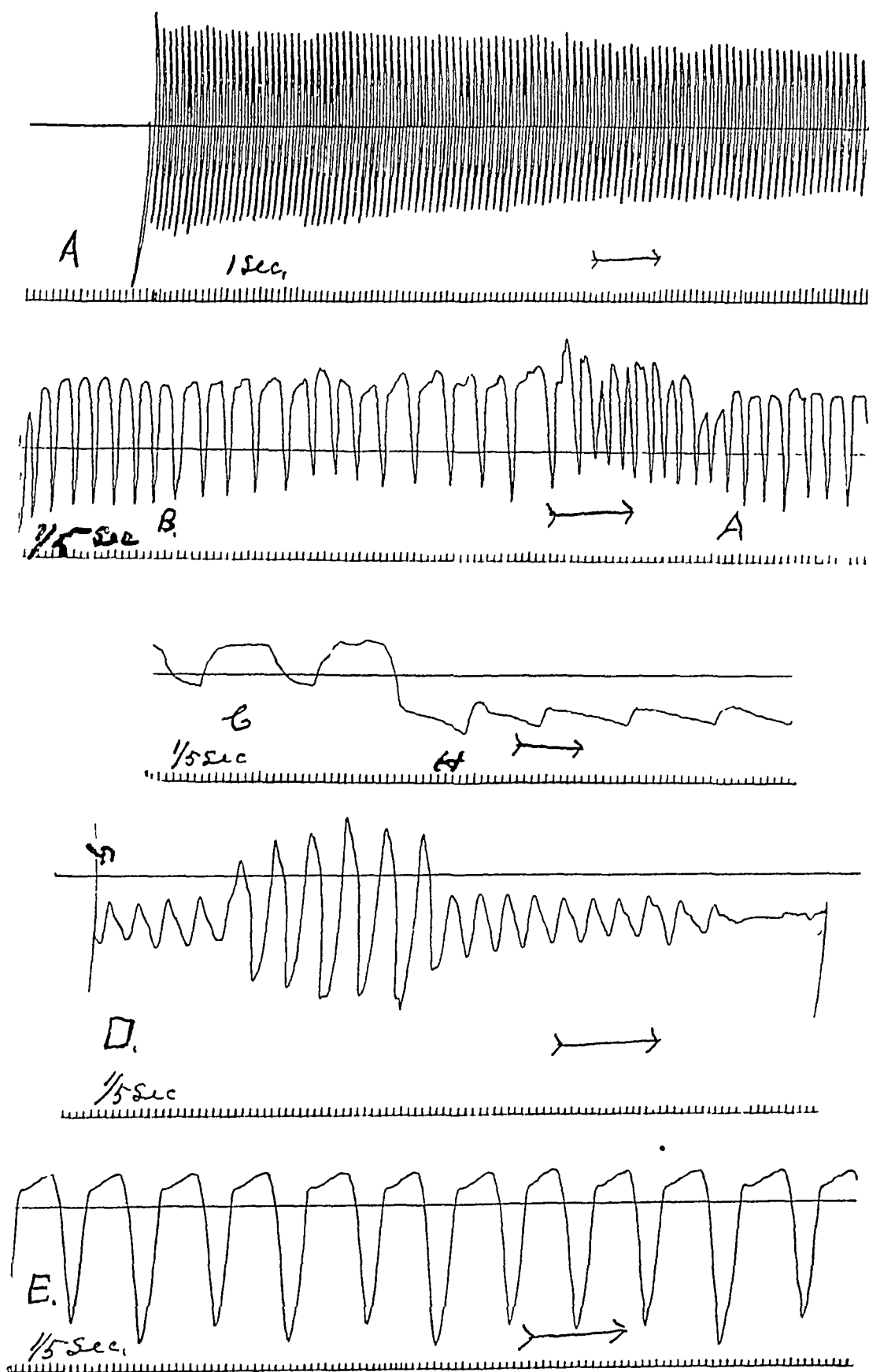


Figure 7

pressure Immediately the inspiratory excursions of intrapleural pressure below the barometric line increased and the expiratory excursions above diminished

The time markings in this tracing are in fifths of a second The horizontal line traces barometric pressure The pressure above the barometric line ranged between 120 and 60 mm of water, and that below between 60 and 10 mm of water, the pressure above the line being greatest when the pressure below was least

In Figure 7, tracing C is from the last part of the tracing shown in B The ten respiratory cycles with the two that preceded H were all alike, having a duration of eight-fifths second for inspiration and twelve-fifths second for expiration The intrapleural pressure in inspiration descended only 15 mm of water below barometric pressure, but during expiration it ascended 40 mm of water above Then as the tracheal cannula was disconnected from the nitrous oxid apparatus at H, the character of the respiration changed The intrapleural pressure remained below the barometric line and during inspiration descended to 50 mm of water

The air was then aspirated from the pleural cavity and 100 cc were obtained, the exact amount injected before the tracing in B and C was begun That the dog was freely exchanging air during this period is shown by the want of hyperpnea as the tracheal cannula was disconnected from the apparatus

In Figure 7, line D is the intrapleural tracing while the dog was freely breathing room air through the tracheal cannula In the six respiratory cycles in which the expiratory pressure goes above the barometric line, the dog's thorax was strongly compressed laterally during expiration between my two hands During this compression, the under surface of the diaphragm was depressed The moderate rise of intrapleural pressure during this procedure gives some idea of the vigor with which expiration was accomplished in the periods when the preceding tracings were made

The dog was then given ether, and a large amount of air admitted to the pleural cavity through the Meltzer cannula The pneumothorax was of such degree that during expiration the entire under surface of the diaphragm projected as a convex dome below the costal borders During this period tracing E, Figure 7, was made The time was in one-fifths of a second, expiration occupying eight-fifths second and inspiration three-fifths second During expiration the intrapleural pressure rose only as high as 40 mm of water above the barometric line, but during the brief inspiration the pressure descended to 180 mm of water below I have in former experiments frequently traced the intrapleural pressure of dogs with severe pneumothorax when morphin and chloretone or morphin and ether were used for anesthesia, and many of the tracings were like this one

The mechanisms involved in breathing against a positive intrapulmonic pressure seem to require further consideration For this purpose another experiment was made with nitrous oxid anesthesia, in which the same apparatus was used as in the preceding one

EXPERIMENT 6—A T-tube was put in the tube connecting with the tracheal cannula, and by means of its lateral branch the intrapulmonic pressure could be traced by a tambour at the same time the intrapleural pressure was recorded by a tambour connected with a Meltzer cannula in the fourth right intercostal space in the mid-axillary line The writing styles of the two tambours were perfectly aligned, so that the intrapulmonic and intrapleural pressures could be compared at any phase of a respiratory cycle

The dog was a terrier weighing 9.5 kilos Nitrous oxid and a little ether were used while the preliminary tracheotomy was performed and the tracheal

cannula fixed in position. Only nitrous oxid and oxygen were subsequently used. The tracing was made while all the muscles involved in respiration were intact.

In Figure 8 the upper line is the tracheal, and the lower line the intrapleural tracing. The horizontal line in each traces the line of barometric pressure. In both, the upstroke traces expiration and the down stroke inspiration. The time marker is in seconds in the slow drum, and in one-fifth second in the fast drum. During the time the tracing was made the abdominal muscles were firmly contracted during expiration, and the respiratory exchange was free between the lungs and the rubber bag containing the anesthetic.

The tambours were calibrated against a water manometer directly after the experiment. At the end of expiration pressure in the pleural cavity equaled 180 mm of water and in the trachea 160 mm. During inspiration the intrapleural pressure attained between 100 and 55 mm of water below the barometric line, and in the trachea at the end of inspiration the pressure was never less than 40 mm of water above the barometric line.

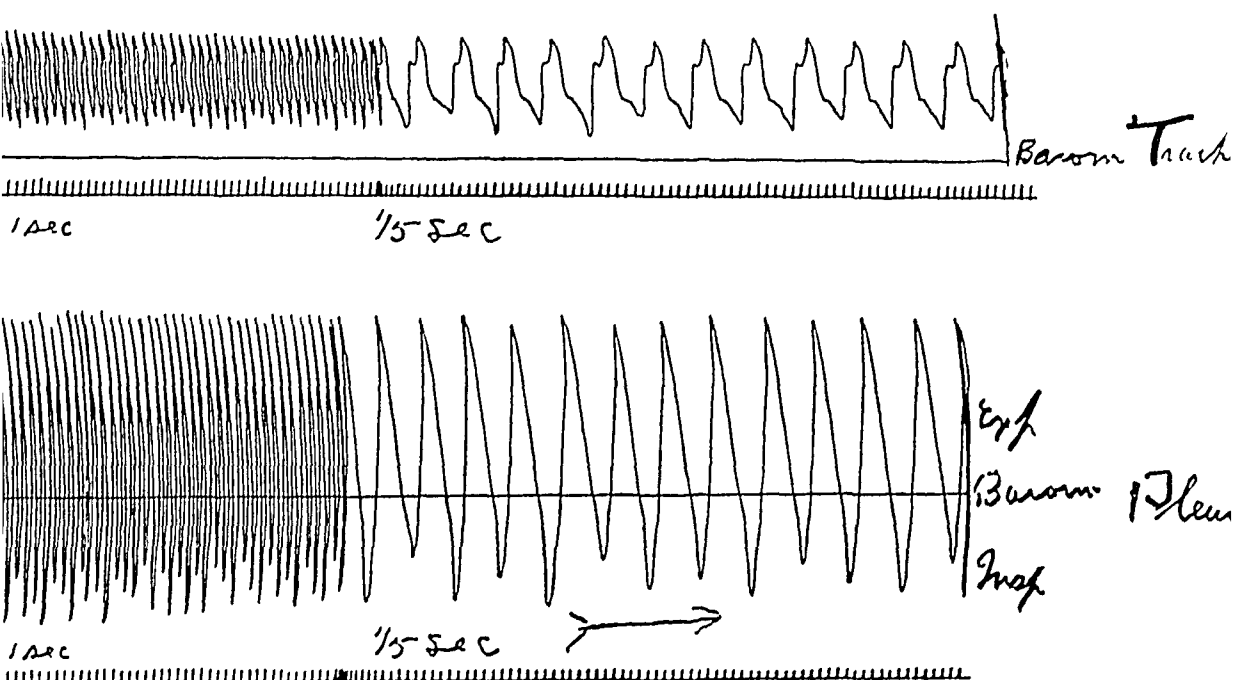


Figure 8

The question might be raised as to how much the expiratory recoil of the distorted thorax can be responsible for the rise in pressure in the pleural cavity. For it may be thought that the recoil of the thorax against the lung distended by intrapulmonic pressure may be responsible for the rise. If we consider the physical conditions at the end of expiration, it is apparent they were as follows. In the pleural cavity there was a pressure of 180 mm produced by the expiratory muscles with the supposed aid from thoracic recoil, and in addition to these factors there was the elastic contraction of the lung, which at the end of expiration balanced a column of water 40 mm high—in all representing an expulsion pressure of 220 mm. These forces were pitted against an intrapulmonic pressure at the end of expiration equal to 160 mm of water. But if we consider for a moment, we shall see that

at the end of an expiratory phase there can be no available force from recoil of the thorax. Instead of recoil in an expiratory direction, there is some potential recoil in an inspiratory direction, as can be shown when air is admitted to the pleural cavity so that barometric pressure is produced. Under such conditions the thorax increases in volume. It is thus apparent that the 180 mm of pressure registered in the pleural cavity at the end of expiration was due wholly to action of the expiratory muscles. This experiment confirms the interpretation of the intercostal source for the intrapleural pressure shown in the preceding tracings of Figure 7. It also furnishes another bit of evidence to show that inspiratory and expiratory forces are equally provided for all the boundaries of the lungs—a conception that is very important for the interpretation of clinical signs pertaining to respiratory excursions of the thorax.

All of the foregoing observations are in direct conflict with two points of view which seem to be generally accepted by physiologists. The prevailing physiologic belief is that widening and narrowing of the intercostal spaces are purposes for employment of the intercostal muscles. It is very obvious from the foregoing observations that if all of the external intercostal muscles are synchronously activated during inspiration, their purpose cannot be to widen all the intercostal spaces, for if the breadth of the intercostal spaces is modified at all during inspiratory excursion, the upper interspaces are narrowed and the lower widened, and during expiration the reverse of this is true. So that obviously, if all the internal intercostal muscles are synchronously activated during expiration, they cannot serve the same purpose in all the intercostal spaces if the modification of the breadth of the spaces is the purpose of their contraction. The chief function assigned to the intercostal muscles by physiologists is the fixation of the sides of the thorax to furnish rigidity to the intercostal spaces. But it was observed in our patient who had paralysis of all the intercostal muscles that he did not in any degree suffer from a want of resistance to atmospheric pressure in the intercostal spaces. The parietal pleura amply serves such a purpose. He did suffer distinctly from an impairment of his vital capacity, but the greatest disability he suffered was the great loss of the intercostal muscles for forcibly constricting and expanding the thorax. If this man were to suffer an attack of bronchiolar hypertonus sufficiently severe to demand an active expiratory effort as well as a vigorous inspiratory effort, he would probably succumb to suffocation. It does not seem possible that he would be able to employ sufficient effort in inspiration and expiration to escape such a fate in view of the violent effort at expansion and constriction of the thorax which is employed by persons with normal musculature in attacks of bronchiolar hypertonus.

MOVEMENTS OF THE FIRST RIB AND STERNUM

This patient with paralysis of the intercostal muscles had an excursion of the sternum and first pair of ribs that is of interest in relation to the normal function of the scaleni and first pair of intercostal muscles. By the use of the scaleni alone, he could increase the circumference of the thorax three-fourths of an inch at the third and sixth intercostal spaces. The increase in circumference below the subcostal angle was due wholly to protrusion of the upper abdomen from descent of the diaphragm. Because of the anchorage of the manubrium and first pair of ribs by the scaleni, these structures are stationary in a normal person with quiet breathing. They move cephalad only in forced inspiration, but in the patient with paralyzed intercostal muscles the manubrium and first rib moved cephalad during quiet breathing, because the normal opposition of the first intercostal muscles to the scaleni was wanting. The balance between the pull of the scaleni and the first intercostal muscles indicates an isometric contraction of the scaleni. The scaleni are activated during quiet inspiration, as indicated by the cephalad movement of the manubrium and first rib in quiet respiration in the case of our patient with paralysis of the intercostal muscles, but in a normal person the origin and insertion of the scaleni are not approximated during activation in tranquil breathing, but without their activation the manubrium and ribs to which they are attached are moved in an expiratory direction during the inspiratory phase. When the scaleni are paralyzed, the manubrium and first, second and third ribs move caudad on inspiration. The fourth rib is stationary, but below that there is an exaggerated movement in a normal direction. A discussion of this subject will be found in a previous publication¹.

Studies of the movements of the first rib and all those below show that in quiet breathing the first rib is not elevated, below the second rib there is no demonstrable variation in the breadth of the intercostal spaces, and isometric contraction prevails in the scaleni and all the external intercostals. Shortening of any of these muscles is not an essential to their employment. They may all be vigorously employed without being shortened, and whether they are shortened or not will depend on the fixation of the muscle at one point of insertion. As mentioned, in the patient who had paralysis of his intercostal muscles the first rib and manubrium moved cephalad during tranquil respiration because of want of fixation of the first rib by normally acting intercostal muscles, and in the child who had paralysis of the scaleni there was distinct narrowing of the upper three intercostal

1 Hoover, C. F. Diagnostic Signs from the Scaleni, Intercostal Muscles and the Diaphragm in Lung Ventilation, *Arch Int Med* **20** 701 (Nov.) 1917

spaces, attended with caudad movement of the upper three ribs when their intercostal muscles were activated during inspiration. This caudad or expiratory movement during the inspiratory phase was due to want of fixation of the upper three ribs by normally acting scaleni.

Because of the normal anchorage of the manubrium and first pair of ribs by the scaleni during inspiration, the distance between two points—namely, on the second rib in the midclavicular and on the tenth in the midaxillary line—is unchanged in thoracic excursion within the range from apnea to maximum inspiration, but normally in tranquil breathing the distance between points on the middle of the clavicle and on the tenth rib in the axillary line is diminished. In our patient, on the left side where all the intercostals were paralyzed, the distance between the clavicle and the tenth rib and between the second and tenth ribs remained the same during quiet and forced breathing.

Under normal conditions the sternum in inspiration is rotated anteriorly on a transverse axis located at the upper border of the manubrium. The ventral elevation of the anterior parts of the second to the fifth ribs, inclusive, carries forward those parts of the sternum to which these ribs are attached, but in our patient the lower end of the sternum was retracted vertebrad with inspiration, because, as the costal borders were drawn toward the median line by inspiratory traction of the diaphragm, the normally acting subcardial diaphragm drew the sternum vertebrad. In inspiration the lower end of the sternum is also retracted when the subcardial diaphragm is flattened sufficiently to give it the mastery over the intercostals. This occurs in enlargements of the heart or the pericardial sac.

FUNCTIONS OF THE INTERCOSTAL MUSCLES

In the beginning of this discussion, a few brief references were made to the history of the study of costal movements and the functions of the intercostal muscles, and the statement was then made that Martin and Hartwell, in 1879, published the only piece of work that has thus far given any experimental support to the theory that the external intercostals had purely inspiratory and the internal purely expiratory functions. The sources of the difficulty lie in the facts that physiologists cramped their minds into believing that all the intercostal spaces were widened during inspiration as an essential part of lung enlargement, but when the intercostal spaces are studied on an animal with an intact thorax, it is found that the spaces remain unchanged in a normal respiratory cycle, and in exaggerated inspiration the upper spaces narrow and the lower widen. If the muscles connecting any two ribs are activated by an electric current, the ribs are approximated when both external and internal muscles or only one of them is intact.

Under the discussion of costal movements it was shown how under

normal conditions the intercostal spaces must all, with the exception of the first, retain a constant breadth in a respiratory excursion ranging between the position of apnea and that of maximum inspiration. But it will also be remembered that, when the scaleni are paralyzed, the first three intercostal spaces are much narrowed during inspiration, the first three ribs move in a caudad direction and the fourth rib remains stationary, while the remaining eight ribs move in a normal direction.

In this relation there is another observation of importance that was made on the patient who had all but the lower four right intercostal muscles paralyzed. When the patient was seated and the examiner, standing behind him, placed a palpating finger of each hand in the tenth intercostal space of either side in the posterior axillary lines, there was a very perceptible difference between the intercostal spaces of the two sides if the patient made a maximum inspiratory effort. On the right side the tenth and eleventh ribs moved in a normal manner and the breadth of the intercostal space was unchanged, but on the left side, where all the intercostals were paralyzed, there was a perceptible widening of the intercostal space and the intercostal structures were retracted and drawn taut as the strong inspiratory effort was made. The patient's scaleni were normal, so when by their maximal activation the upper thorax was drawn upward, the traction applied to the upper two ribs by the scaleni served to elongate the thoracic wall of the entire left side by a very slight but perceptible widening of the intercostal spaces.

When in a seated position this patient made a strong inspiratory effort, the circumference of his thorax at the third and sixth interspaces increased three-fourths of an inch, although all the intercostal muscles of both sides in these parts were paralyzed. This increase in circumference was due entirely to the scaleni, which by their attachments to the first and second ribs not only drew these ribs upward but exerted a cephalad traction on all the ribs below by means of the connections through the parietal pleura, which is capable of very slight extensibility. The increase in circumference of the upper three quarters of the thorax was accomplished by the action of the scaleni only, and as already shown it would be impossible to elevate the ribs in their parallel relation without narrowing the intercostal spaces or retaining a constant breadth between them. The very limited extensibility of the parietal pleura allows only a slightly perceptible broadening of the spaces. It will be remembered that in this patient all the intercostal muscles of the left side and all but the lower four on the right were paralyzed. When a tape, fixed on the third rib in the left midclavicular line, was drawn taut to the tenth rib in the left midaxillary line, the distance between these two points was very slightly increased.

by a maximum inspiration. When during a forced inspiration the upper end of the tape was fixed on the middle of the clavicle, the distance between the clavicle and the point on the tenth rib showed about the same increase. On the right side, where the lower four intercostals only were active, when symmetrical measurements were made in the same manner, the distance from the third to the tenth rib in inspiration was found to be shortened by a distance equal to the breadth of one interspace, and the distance from the clavicle to the tenth rib was diminished as in normal persons.

When the lower intercostal spaces of the right side were examined, the eighth intercostal space was found to be narrower than that immediately above and below. This was due to paralysis of the seventh intercostal muscle and the downward traction of the eighth rib by the intact muscles of the eighth interspace. During inspiration the ninth rib moved with vigor in a normal direction, but its excursion was perceptibly less than that of the tenth, eleventh and twelfth. After a little practice in palpating ribs, the examiner will readily distinguish between the movement of a rib that passively yields to the traction of its intercostal attachments and a movement that is conferred on it by action of its attached intercostal muscle.

The effect of paralysis of an external intercostal muscle on the breadth of its interspace is shown by a very simple experiment. The ribs and intercostal muscles are exposed in the middle part of one side of a dog's thorax and the external intercostal muscle of the eighth interspace severed in its middle for its entire extent. During tranquil respiration the eighth space is then seen to widen during inspiration by an upward movement of the eighth and a lesser downward movement of the ninth rib.

It is quite clear, then, that action of the intercostal muscles either narrows or preserves the upper intercostal spaces unchanged, and the only interspaces that are widened by inspiration are those spaces between the lower chondral cartilages as they form angles with their respective ribs to pass cephalad toward their junction with the sternum. It now remains to be shown how the external and internal intercostal muscles are brought into requisition by different kinds of respiratory movements.

A normal person can aspirate a column of mercury 90 mm., and blow a column 100 mm. high. Aspiration is done by the diaphragm, intercostals and scaleni, compression of the lungs, by the abdominal muscles and the intercostals. When the intercostals were paralyzed, a man who normally should be able to blow a column of mercury 100 mm. was able with powerful abdominal muscles to blow a column only 50 mm. high, and aspirate by his diaphragm and scaleni a column only 46 mm. These results proved that in a normal person the share of the

intercostal muscles in forced inspiration is equal to that in forced expiration, and, therefore, in the act of compression, all the intercostal muscles are employed both in depressing and in elevating the ribs if the maximum inspiratory and maximum expiratory efforts are made. So if approximation of the ribs by intercostal action is to be observed, it is advisable to study the movements of an adjoining pair of ribs when they are cut away from their costal attachments above and below and freely respond to activation of the muscles connecting them. By severing the connecting external muscle in one instance and the internal in another, we are able to see under what respiratory conditions both the external and internal muscles are brought into action. However, if the threshold of employment for the internal intercostals only is to be studied, the thorax can be left intact and the external intercostals severed for their entire extent in two neighboring intercostal spaces. The dog is then made to rebreath an atmosphere with a high carbon dioxide content to induce hyperpnea, and by applying compression to the tube connecting the bag with the tracheal cannula, the behavior of these muscles can be brought out when great effort in expansion and compression of the lungs is employed.

The results obtained by animal experiment in the study of intercostal muscle employment vary with the anesthetic and the depth of anesthesia, and also with the stage of exhaustion of the respiratory innervation. The intercostal muscular response also varies with the amount of tidal air demanded by the respiratory need and with the resistance to inspiration and to expiration. To get the best results the respiratory threshold should be raised as little as possible by the use of anesthesia. The less the respiratory threshold is raised the greater is the alertness and vigor in the respiratory efforts that follow when the animal breathes a high concentration of carbon dioxide or is made to work against resistance to the entrance and exit of air.

THRESHOLDS FOR EMPLOYMENT OF THE EXTERNAL AND INTERNAL INTERCOSTALS

Experiments were made to gain information about the thresholds of employment for the two sets of intercostal muscles in inspiration and expiration.

EXPERIMENT 7—After the ribs and intercostal muscles have been exposed over one side of a dog's thorax, the external intercostal muscle in the eighth interspace is severed in the middle intercostal line from its anterior border to the vertebra. Then, while the animal is tranquilly breathing room air, the space between the two ribs united only by the internal intercostal muscle widens with inspiration, while the spaces above and below remain constant. However, there is thus far no evidence of activation of the exposed internal intercostal muscles. The tracheal cannula is then connected with a bag containing 75 per cent oxygen and 25 per cent carbon dioxide. With the ensuing hyperpnea the dog is compelled to speed up his respiratory and expiratory

phases, and the tidal air is greatly increased, so that the expiratory excursion of the thorax exceeds that of the position of apnea. The exposed internal intercostal muscle is then seen to contract vigorously during expiration as the thorax is circumferentially constricted. But thus far there is no evidence of activation of the internal intercostal muscle during inspiration. Apparently the external intercostal muscles are still adequate to move the ribs into their position of maximum inspiration so long as there is no resistance to the entrance of air, but when the tube connecting the bag and the dog's tracheal cannula is narrowed so that a great inspiratory effort is demanded in the presence of hyperpnea, the exposed internal intercostal muscle is brought into action to aid the inspiratory effort. With the intact thorax this action cannot be shown by any other sign than that the two ribs which are connected by only their internal intercostal muscle are no longer separated during the inspiratory effort as they were in tranquil inspiration.

This indicates that the threshold for expiratory employment of the internal intercostal muscle is lower than that for its inspiratory employment. We must consider too that, although the internal muscle was brought into service with expiration before the tube connecting the trachea and bag was narrowed, the abdominal muscles had not yet been actively contracted during expiration, and thus far it has not been proved that the external intercostal muscles are ever employed in expiration.

To investigate the question of the expiratory use of external intercostals, another dog experiment was conducted in the following manner:

EXPERIMENT 8—After a preliminary dose of $\frac{1}{4}$ gram morphin, under ether anesthesia the ribs and intercostals of the lower right thorax were exposed. The sixth and eighth intercostal spaces were cut through for their entire extent and artificial respiration employed. The seventh and eighth ribs were then cut at their costochondral junctions and the internal intercostal muscle was severed through its midline for its entire extent, so that the two ribs were united by the external intercostal only. The two remaining parts of the ribs were held in their normal position with the connecting external intercostal muscle slightly taut. Artificial respiration was then suspended, and, as active respiratory movements by the dog were begun in response to suffocation, there was at first no evidence of expiratory activation of the isolated external intercostal muscle, but as the vigor of the respiratory efforts was increased and the abdominal muscles were strongly activated in expiration, as shown by the forceful upward displacement of the vault of the diaphragm and firm expiratory contractions of the abdominal muscles, the external intercostal muscle which alone united the two isolated ribs, contracted very actively and approximated the ribs. When the abdominal muscles were not activated in expiration, the isolated external intercostal did not contract.

This experiment was repeated several times and indicates a synergic employment of the abdominal muscles and external intercostals in a forced expiratory effort.

Experiment 9, when taken alone, would confirm the observations of Martin and Hartwell, and without further observations would confirm the Hamberger theory that the external intercostals have a purely inspiratory and the internals a purely expiratory function.

EXPERIMENT 9—After the usual preparatory procedures, the sixth and ninth intercostal spaces were cut through their entire extent, and the seventh, eighth and ninth ribs were cut at their costochondral junctions. In the seventh interspace the internal intercostal muscle was severed midway between the ribs for its entire extent, and the same was done for the external intercostal muscle in the eighth interspace. We then had the seventh and eighth ribs united only by the external intercostal, and the eighth and ninth by the internal intercostal. Artificial respiration was suspended and the arches of the seventh and ninth ribs were held by the hands in their normal anatomical position on the vertebrae. Slight traction was employed to keep the remaining intercostal muscles slightly taut. Then in inspiration, as suffocation induced active respiratory movements, the eighth rib was drawn upward by the external intercostal muscle, which alone united it to the rib above, and during expiration the eighth rib was actively drawn toward the ninth rib, to which it was united by the internal intercostal only.

This procedure was repeated many times, until the respiratory function was greatly exhausted, and then the expiratory contraction of the internal intercostal ceased when the inspiratory action of the external intercostal was still quite active. During the experiment, however, at no time in expiration were the abdominal muscles contracted, and, therefore, there was no expiratory action of the external intercostals, and furthermore, we could not excite the internal intercostals to an inspiratory effort by offering any resistance to inspiration, as was done in the first experiment when the animal was breathing 75 per cent oxygen and 25 per cent carbon dioxid with a closed thorax and against a strong resistance to the entrance of air into the lungs.

These experiments show that the external intercostals under all respiratory conditions are activated during inspiration, and that in tranquil respiration none of the intercostal muscles are employed in passive expiration. During active expiration the internal intercostals are brought into action when the abdominal muscles are not yet needed, but when active expiration enlists the aid of the abdominal muscles, the external intercostals are synergically activated with them.

With an open thorax the conditions forbid the employment of measures that will exceed the threshold for the inspiratory use of the internal intercostals, but so far as could be determined with a closed thorax, the internal intercostals were brought into service when the animal was made to inspire against a high resistance in the presence of great hyperpnea induced by rebreathing an atmosphere consisting of 75 per cent oxygen and 25 per cent carbon dioxid. When we consider, however, that a normal person can by the use of his scaleni, intercostals and diaphragm aspirate a column of mercury 90 mm high, and that by use of his abdominal muscles and intercostals the air in the lungs can be compressed to balance a column of mercury only 10 mm higher, there is good inferential evidence to prove that in a forced inspiratory effort both sets of intercostals are employed, for we know that both external and internal intercostal muscles are employed in efforts at

pulmonary compression when the abdominal muscles are for this purpose brought into use. It must also be remembered that the man who had all but the lower right four intercostals paralyzed was able to raise the pressure in his lungs to a height of 50 mm of mercury by use of his abdominal muscles, and should have raised it to 100 mm had his intercostal muscles been normal. By use of his *scaleni* and his diaphragm, he was able to aspirate a column of mercury 46 mm high. As we know that the loss in power for constricting the thorax was due to paralysis of both external and internal intercostal muscles, there is good reason to believe that the loss of aspirating power was not due to paralysis of his external intercostals alone, as we should have to believe if the internal intercostals are regarded as having a purely expiratory function.

The foregoing clinical and experimental observations show that the muscular boundaries of the lung—viz, the intercostal muscles and diaphragm—with the aid of the *scaleni* and abdominal muscles, supply a uniformly distributed power and capacity for expansion and compression over the entire lung surface, and also that the power available for expansion is about equal to that for compression. The synergic use of all these muscles provides the lung with a motor organism that is like what the heart would have if it were endowed with equal diastolic and systolic powers.

The power for circumferential compression and expansion of the lung is equal to the available power for longitudinal compression and elongation. It is clearly proved that both external and internal intercostals are employed to obtain the maximum circumferential compression, and the corollary from this demonstration is that both external and internal intercostals are employed to obtain the maximum circumferential expansile force. The maximum expansile capacity can be obtained without the use of the internal intercostals if there is no resistance to the entrance of air, but when the maximum expansile force is required, the internal intercostals are brought into use. Furthermore, these clinical and experimental observations show that the motor agencies for the ribs are directed wholly toward modifying the circumference of the thorax, and that any changes in the breadth of intercostal spaces are merely incidental to intercostal muscular action and not the purpose of it.

INTEGRATION OF THORACIC MUSCLES

The foregoing discussion shows the external and internal muscles to be employed during both inspiration and expiration, but how they can equally serve both is not yet apparent. The intercostals alone cannot be responsible for the smooth and orderly manner in which the purposeful excursions of the ribs are displayed during the entire cycle of forced breathing. Thus far the only demonstrated intrinsic effect

of intercostal action is to narrow all the intercostal spaces. If this action during both inspiration and expiration were not modified by the actions of other muscles, the results during both phases of respiration would be a disorderly and fruitless procedure that would contribute nothing to either expansion or compression of the lungs. Which muscles serve to integrate the intercostal muscles for an inspiratory effort and which convert their action into an integrated expiratory effort, are questions that demand an answer.

The inspiratory excursion of the upper thorax of our patient with intercostal paralysis was a lifeless, passive movement, like the expansion of the thorax of a cadaver when the sternum is pulled cephalad. The expansion below the level of the subcostal angle was due largely to the inspiratory descent of the diaphragm. On the left side, where all the intercostals were paralyzed, all the ribs moved slightly cephalad in response to action of the *scaleni* which drew the first and second ribs in a cephalad direction, and all the ribs below passively followed as a result from traction on the broad sheet of parietal pleura, which is firmly united to the ribs at all the costal spaces. On the right side, the same kind of movement was apparent as far down as to the ninth rib, but the last four ribs moved in a normal manner because of the anchorage from above that was transmitted along the parietal pleura by the normally acting *scaleni*.

The want of integration of the upper three intercostal muscles with the inspiratory act is clearly demonstrated when the *scaleni* are paralyzed. These intercostal muscles are activated with all the others during inspiration, but instead of inspiratory inflation there is deflation of the underlying lungs. This is so pronounced that the consequent rebreathing between the upper and lower lungs demands an exaggerated excursion of the lower to compensate for the defective excursion of the upper thorax. This phenomenon was so pronounced in the child referred to above that it led to calling medical counsel. In this child the manubrium and upper three ribs moved strongly caudad during expiration. The fourth rib was stationary during the whole respiratory cycle, while from the fifth rib downward there was an exaggeration of the normal excursion.

When in the dog the attachments of the *scaleni* to the upper three ribs were cut, the same costal movement as seen in the child was reproduced, but with the ribs exposed a more satisfactory inspection could be made. The upper three ribs not only moved in an expiratory direction during inspiration, but there was a want of integration in their excursions. They moved in a disorderly manner. The first rib moved caudad and so did the second, but the first intercostal space was narrowed. The second intercostal space was obliterated by the upper border of the third rib, which overrode the lower border of the second

The third interspace was also narrowed. In this relation one must recall the fact that in orderly forced expiration all these intercostal spaces are widened as the ribs move caudad, and in the inspiration of quiet breathing these upper three spaces are unchanged in width. When the upper end of the manubrium was anchored by grasping it with forceps and holding it in the position it took at the end of expiration, then the upper four ribs moved in their normally integrated manner. It has been shown in Experiments 5 and 6 that, when the diaphragm is paralyzed and all the attachments of the abdominal muscles to the thorax are severed, it is still capable of great inspiratory and expiratory excursions, the tidal air is comparatively large, and the intrinsic muscles of the thorax cause marked compression of the lungs.

In these experiments the iliocostal muscles were cut between the ileum and last rib. The only integrators that under such experimental conditions could order the inspiratory and expiratory effect of the intercostals were the scaleni, the serrati postici, superior and inferior, and the triangularis sterni. As already shown, the function of the scaleni during quiet respiration is essential for the orderly action of the upper three intercostal muscles, although in such breathing the upper border of the manubrium and first rib are stationary. Without the anchorage of the scaleni, by their isometric activation the upper three ribs move in an expiratory direction during the inspiratory phase and the upper parts of the lungs are deflated. To determine if the serratus posticus inferior may not serve the same purpose for the lower thorax during forced expiration that the scaleni serve for the upper. Experiment 10 was performed.

EXPERIMENT 10—A dog was anesthetized with nitrous oxid and a cannula put in the trachea through which the anesthetic was afterward continued. The same apparatus was used as described in the preceding experiment. The dog was turned on his right side and the muscles over the lower right side of the thorax exposed. The latissimus dorsi was cut and the erector spinae exposed. Along the course of each of the last four ribs an incision was made down to the surface of the rib from beneath the lateral border of the erector spinae, well beyond the lateral extensions of the serratus posticus inferior. By this means the function of the latter muscle was eliminated, but the intercostal muscles were preserved. The linea alba was then cut from the diaphragm to the pubis and a transverse incision on both sides eliminated all the abdominal muscles and the iliocostals in expiration. The triangularis sterni was still intact but it could not play any part in the expiratory excursion of the last four ribs. The conditions of the two sides of the thorax were the same with the exception that on the right the serratus posticus inferior was eliminated and on the left it was intact. The last four ribs could be palpated on both sides through the intervening diaphragm, which was relaxed during expiration. By placing alternately the four finger tips of either hand on the inner surfaces of the last four ribs of the right and left sides, a decided difference could be detected in the manner of their expiratory excursions. On the right side where the serratus posticus inferior was wanting, the last four ribs were approximated during expiration much in the same manner as the four fingers are drawn together by the interossei. On the left side the last

rib and the three above it were drawn forcibly in an expiratory direction, and the approximation of the ribs during expiration was much less than on the right side. The disordered movement of the lower right ribs in active expiration was analogous to the disorderly movement of the upper ribs during inspiration when the scaleni were eliminated. In the middle and upper parts of the thorax it is not possible with the thorax intact to produce an isolated function of the intercostal muscles during expiration on account of the *triangularis sterni*, which in the dog is a strong muscle that is a continuation of the *transverse abdominis*.

To conclude the experiment, the diaphragm was freely opened and artificial respiration was continued a short time by compressing the oxygen bag that was put in communication with the tracheal cannula. By inserting the hand in the thorax the *triangularis sterni* could be felt to contract strongly during expiration. The sternal ends of the ribs and the costal cartilages were by its action vigorously drawn in an expiratory direction, but during inspiration the muscle was relaxed. While the thorax was intact, the last four ribs on both sides moved cephalad in inspiration and the intercostal spaces were widened.

With these experiments it seems clear how the integrative actions of the intercostals during inspiration are made to serve alternately for inflation and deflation of the lungs. During inspiration the scaleni and *serrati postici*, superior, supply the necessary cephalad anchorage for the entire length of the thorax, and in active expiration when the abdominal muscles are eliminated, the caudad anchorage for the bottom ribs is supplied by the *serratus posticus inferior*, and the caudad traction for the entire cuirass is supplied by the *triangularis sterni*. Until the *triangularis sterni* and those parts of the ribs to which it is attached were palpated during active expiratory efforts, the important function played by this sheet of muscle was greatly underestimated.

By these studies the conviction is gained that, in the orderly, integrated function of the scaleni and the intrinsic muscles of the thorax, we have a well ordered action that suggests the progress of a peristaltic wave, such as prevails along the gullet, where the action remains the same but the result is deglutition or vomiting as the gradient is caudad or cephalad. In the case of the intercostal muscles, their action is the same in inspiration and expiration, just as Vesalius said nearly four hundred years ago, but they aid expansion or constriction of the thorax according to the gradient, which is determined for inspiration by synchronous activation of the scaleni and *serratus posticus superior* and for expiration by the *serratus posticus inferior*, *triangularis sterni*, and abdominal muscles.

By this statement it is not intended to convey the idea that succession in the action of the intercostal muscles has been proved. In fact, my own experiments directed toward investigation of this question have thus far indicated that in inspiration all the intercostals are synchronously activated.

THE ESTIMATION OF NORMAL VITAL CAPACITY

WITH ESPECIAL REFERENCE TO THE EFFECT OF POSTURE *

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For controlling a contemplated experimental research on orthopnea we found it necessary to establish some standards for normal vital capacity in healthy persons in both the sitting and the lying position. In the literature many observations were found on the vital capacity under almost every other conceivable experimental condition, but although the statment is frequently made that a normal person can breathe more when sitting erect than when recumbent, we discovered no attempt to estimate the percental differences due to posture. Experimental investigation doubtless began with the work of John Hutchinson,¹ who gives data to show that the vital capacity is smaller in the supine position than in the erect. A few observations were made by us on individuals about the laboratory, and the results were found to vary considerably, that is, some could after a maximum inspiration expire as much lying as sitting, a few could expire more, and the majority were not able to do nearly so well lying as sitting. As these observations seemed to refute partially at least the idea that the vital capacity is always smaller in the lying position, it was decided to check the whole subject on a large series of normal people.

The investigation, entered into along the lines just described, widened into an inquiry as to the best basis for comparison in the estimation of vital capacity. Our data show very clearly that body surface, as determined by the linear formula of Du Bois, is a far more accurate and constant index of comparison than is height or weight, or certain measurements of the volume of the chest as recently advocated by Lundsgaard and Van Slyke.² Our data also seem to bear out the physiological fact, well established by Stewart³ and others, that in animals the weight of the lungs bears a very definite and constant ratio to the skin surface.

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1 Hutchinson, J. *Med Chir Tr* **29** 137

2 Lundsgaard and Van Slyke. *J Exper M* **27** 65, 1918

3 Stewart, G. N. *Am J Physiol* (In press)

We were able to make observations on 290 normal people—144 women and 146 men. The women were all healthy nurses, who had had a recent physical examination, and whose ages varied from 20 to 30 years. The men were practically all medical students, also ranging in age from 20 to 30 years, they had had a recent physical examination, and we were sure that they were normal. We were working with an intelligent lot, and we feel certain that the end result was the maximum effort in each case. When there was any doubt in our minds as to the accuracy of any determination, it was not included in our totals.

TABLE 1—MALES GROUPED ACCORDING TO WEIGHT IN KILOGRAMS

Weight in Kilos	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C c	Percentage Difference	No not Falling Within + or — 10% of Average
		Sitting, C c	Lying, C c			
55 to 65	49	4,272	4,017	255	5.9	13
65 to 75	61	4,661	4,440	221	4.7	17
75 to 85	26	4,974	4,674	300	6.0	5
85 to 95	10	5,379	5,109	270	5.0	7
Total	146	Average difference			5.5	12 or 28%

TABLE 2—MALES GROUPED ACCORDING TO HEIGHT IN CENTIMETERS

Height in Centimeters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C c	Percentage Difference	No not Falling Within + or — 10% of Average
		Sitting, C c	Lying, C c			
150 to 160	2	3,721	3,590	131	3.5	0
160 to 170	37	4,197	3,963	234	5.6	11
170 to 180	82	4,641	4,411	230	4.9	21
180 to 190	25	5,366	5,070	296	5.5	8
Total	146	Average difference			4.9	40 or 27%

TABLE 3—MALES GROUPED ACCORDING TO BODY SURFACE

Body Surface in Sq. Meters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C c	Percentage Difference	No not Falling Within + or — 10% of Average
		Sitting, C c	Lying, C c			
1.6 to 1.7	15	4,008	3,808	200	5.0	6
1.7 to 1.8	46	4,303	4,102	201	4.6	3
1.8 to 1.9	46	4,609	4,363	246	5.3	6
1.9 to 2.0	27	5,150	4,858	292	5.6	7
2.0 to 2.1	12	5,565	5,250	315	5.7	3
Total	146	Average difference			5.2	23 or 16%

METHOD OF STUDY

With an ordinary spirometer three estimations were made on each individual in the sitting position and three in the lying position. The largest amount which an individual expired sitting or lying, out of three attempts made in each position, was the figure which we used in computing our totals. All of the subjects were dressed in ordinary clothing, and no deductions were made in recording weights and there

was nothing taken from the height because of shoes. It is quite probable that some of the estimations in the case of the nurses were influenced by the fact that corsets were not removed.

Differences Due to Posture—It will be seen from the tables that, when the vital capacities of all these 290 normal persons are averaged, there is for all groups approximately 5.5 per cent less vital capacity in the recumbent position than in the upright. Some few breathed somewhat better lying, and some were able to expire about as much lying as sitting, but it is certain that about 80 per cent of people breathe somewhere near 6.5 or 7 per cent less in a reclining position, and the remaining 20 per cent breathe either more or about the same.

TABLE 4—FEMALES GROUPED ACCORDING TO WEIGHT IN KILOGRAMS

Weight in Kilos	Number Studied	Vital Capacity		Difference Be- tween Sitting and Lying, C c	Percentage Difference	No. not Falling Within + or - 10% of Average
		Sitting, C c	Lying, C c			
45 to 55	48	2,908	2,729	179	6.1	17
55 to 65	68	3,146	2,945	201	6.3	20
65 to 75	21	3,132	2,923	209	6.6	9
75 to 85	7	3,356	2,871	485	14.4	2
Total	144	Average difference			8.3	48 or 33%

TABLE 5—FEMALES GROUPED ACCORDING TO HEIGHT IN CENTIMETERS

Height in Centimeters	Number Studied	Vital Capacity		Difference Be- tween Sitting and Lying, C c	Percentage Difference	No. not Falling Within + or - 10% of Average
		Sitting, C c	Lying, C c			
150 to 160	29	2,945	2,714	131	4.4	9
160 to 170	98	3,066	2,884	182	5.9	26
170 to 180	17	3,506	3,256	250	6.9	7
Total	144	Average difference			5.4	42 or 29%

TABLE 6—FEMALES GROUPED ACCORDING TO BODY SURFACE

Body Surface in Sq. Meters	Number Studied	Vital Capacity		Difference Be- tween Sitting and Lying, C c	Percentage Difference	No. not Falling Within + or - 10% of Average
		Sitting, C c	Lying, C c			
1.4 to 1.5	11	2,688	2,520	168	6.2	3
1.5 to 1.6	45	2,939	2,804	135	4.6	7
1.6 to 1.7	54	3,108	2,926	172	5.5	9
1.7 to 1.8	21	3,246	3,046	200	6.1	6
1.8 to 1.9	15	3,400	3,148	252	7.4	1
Total	144	Average difference			5.9	26 or 18%

We attempted to discover whether differences in types of chest would account for these variations between lying and sitting, but the only thing which seemed to point to some different response was in the case of women of the rather obese type. The obese women sometimes breathed as much as 20 per cent less lying than sitting. This is quite noticeable in Table 4, in which it will be seen that females weighing from 75 to 85 kilos averaged 14.4 per cent less in the lying

position We had no men in our series who were comparable to these females Except for this disparity between the sitting and the lying position of fleshy females, it was found that, when vital capacity was taken in the two positions, all types of chest seemed to respond to the experimental conditions in much the same fashion

Comparison with Height and Weight—As to whether weight or height is the better index of comparison for the vital capacity was debated by John Hutchinson prior to 1846 He made observations on the vital capacity of 2,130 persons, all of whom were normal except sixty These observations were made on people from all walks of life It was his opinion that comparison of the vital capacity with the height of the individual was the most satisfactory method However, Hutchinson as well as subsequent observers noted that the vital capacity in people of the same height varied tremendously, although it was noted by all that it was much more constant when compared with the height than with the weight

Our data readily bear out the contention of John Hutchinson and subsequent workers that vital capacities of persons of the same weight vary widely (Tables 2 and 5) In the females there were 33 per cent who did not fall within plus or minus 10 per cent of the average when compared by weight, and there were 28 per cent of the males who varied rather widely from their average Our figures also agree with those of John Hutchinson in showing that a comparison of the vital capacity with the height is more accurate than with the weight However, 27 per cent of the females and 28 per cent of the males when so compared missed the average by more than plus or minus 10 per cent This error is more apparent than real, when comparison is made with height, for in those who missed the average of their respective groups, the variations were not great, while in the comparison by weight, many missed their group by hopeless differences

Comparison with Chest Measurements—Recently Lundsgaard and Van Slyke have contended that chests measured according to certain formulas and found to agree in size would more nearly have the same vital capacity than would the chest of persons of the same height However, Peabody ⁴ has denied this contention of Lundsgaard and Van Slyke Peabody's investigations show that persons of the same height have more nearly the same vital capacity

Comparison with Body Surface—Our data clearly demonstrate that it is not height or weight or chest measurements but body surface that is by far the most constant and exact standard for comparison Dreyer ⁵ recently published data which seem to support this contention,

⁴ Peabody, F W Oxford Med **1** 399

⁵ Dreyer, G Lancet **2** 227 1919

but the number of observations which he made is small. The data which West⁶ accumulated on a comparison of vital capacity in normal individuals with the body surface agrees quite closely with our figures. In our observations (Tables 3 and 6) it will be seen that when the comparison is made with the body surface as estimated by the "linear formula" of Du Bois, only 18 per cent of the females and 16 per cent of the males missed the average for their respective group by plus or minus 10 per cent. Furthermore, there were scarcely any of either the women or the men who missed by more than 15 per cent. In addition it should be noted that most of those who did miss their respective group were the extremes in body surface—that is, those who had the smallest or those who had the greatest. For if we take the group of females whose body surface is from 1.5 to 1.7 square meters, which represents the size of approximately 80 per cent of the women in our series, then we find that only 16 per cent missed their respective group averages by plus or minus 10 per cent. In the case of the males, it will be seen that approximately two thirds fall in the two groups whose body surface is from 1.7 to 1.8 and from 1.8 to 1.9 square meters, and there were slightly fewer than 10 per cent of these who missed their average by more than plus or minus 10 per cent.

The males in this group seemed to be distinctly more constant in the grouping of their vital capacity by body surface than were the females. This may be in part due to the fact that the females were not required to remove their corsets.

It will be seen from Tables 3 and 6 that in the case of females the vital capacity goes up about 175 c.c. with each increase of 0.1 square meter in body surface, while in the case of males the vital capacity advances about 350 c.c. for each gain of 0.1 square meter. Therefore, to get the normal total vital capacity of a woman of the age included in our group, it is only necessary to remember that a body surface of from 1.4 to 1.5 square meters indicates a vital capacity of 2,700 c.c., and that for each increase in body surface of 0.1 square meter, 175 c.c. must be added. In the case of a male, with a body surface of from 1.6 to 1.7, the average vital capacity is 4,000 c.c. For each increase in body surface of 0.1 square meter, add 350 c.c., which will give the approximate average for each group.

Then, from our series the advantage of reckoning the vital capacity from the body surface is apparent. There are, perhaps, few clinical methods of precision which do not have a greater range of error than plus or minus 15 per cent. After all, for comparative purposes one wants the lower range of normal, and while 16 per cent of the males and 18 per cent of the females missed their

6 West, Howard F. *Arch Int Med* 25:306 (March) 1920

respective average, only about half of those who missed the average of their respective group were below, and these are after all the only important ones to consider. So that, in reality, for comparison purposes only 8 per cent of males and 9 per cent of females missed their respective grouping by body surface by more than minus 10 per cent.

CONCLUSIONS

1 After computing the averages of all estimations on 290 normal men and women, we found that there was 5.5 per cent less vital capacity in the lying than in the sitting position.

2 We noted also that about 80 per cent of all individuals breathed 6 or 7 per cent less when lying, and that 20 per cent, breathed about the same or more. We noted no difference in chest conformation to account for these variations. The only thing we did note which seemed to point to a different response from certain types of chest was in the case of obese women. In every instance the fleshy female breathed about 15 per cent less lying than sitting.

3 According to our observations, individuals of the same sex and body weight have very great differences in their vital capacity, individuals of the same sex and height have more nearly the same vital capacity, while individuals of the same sex and body surface are surprisingly alike in their vital capacity. It was found that only about 8 per cent of all males and about 9 per cent of all females, when grouped according to body surface, missed their respective group average by more than minus 10 per cent.

4 From our totals we may conclude that a female from 20 to 30 years of age, with a body surface of from 1.4 to 1.5 square meters, has a vital capacity of 2,700 c.c., and for each gain of 0.1 square meter in body surface the vital capacity goes up about 175 c.c. A male from 20 to 30 years of age, with a body surface of from 1.6 to 1.7 square meters, has a vital capacity of about 4,000 c.c., and with each gain of 0.1 square meter the vital capacity goes up 350 c.c. From these data we can conclude that a normal male between the ages of 20 and 30 has a vital capacity of 2.5 liters per square meter of body surface, and that a normal female between 20 and 30 has a vital capacity of 2 liters per square meter of body surface.

THE CAPILLARY BLOOD PRESSURE IN ARTERIAL HYPERTENSION *

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Although the anatomy and physiology of the capillaries have been of interest to physiologists for many years and have been the subject of many investigations, their importance in the dynamics of the normal circulation and in the study of pathologic states is just beginning to be appreciated. The studies of Krogh¹ and Richards² on the response of the capillaries to the functional needs of the tissues, those of Dale³ and Cannon⁴ on the importance of the capillary mechanism in shock, the researches of Weiss⁵ and his co-workers on the morphology of the capillaries and the character of the capillary flow in disease, and the studies of Kylan⁶ and Danzer and Hooker⁷ on the capillary blood pressure have within the last few years pointed out how essential a knowledge of the capillary function is to the clinician in his study of disease. The concept that the cardiovascular system is primarily adapted to maintain the blood flow in the capillaries, where the exchange of gases, food elements and waste between the tissues and the blood takes place, is a very fundamental one and one that cannot be overemphasized. It must further be recalled that the capillaries themselves play an active part in the maintenance of an adequate blood supply to the tissues, that they exhibit contractility and dilatability in response to nervous and metabolic stimuli and so assist in regulating the blood flow according to the needs of the tissues.⁸

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1 Krogh, A. The Supply of Oxygen of the Tissues and the Regulation of the Capillary Circulation, *J Physiol* **52** 457 (May) 1919, Studies on the Capillariomotor Mechanism. I. The Reaction to Stimuli and the Innervation of the Blood Vessels in the Tongue of the Frog, *J Physiol* **53** 399 (May) 1920

2 Richards, A. N. Kidney Function, *Am J M Sc* **163** 1 1922

3 Dale, H. H. Capillary Poisons and Shock, *Bull Johns Hopkins Hosp* **31** 257, 1920

4 Cannon, W. B. A Consideration of the Nature of Wound Shock, *J A M A* **70** 611 (March 2) 1918

5 Weiss, E. and Dieter, W. Die Stromung in den Kapillaren und ihre Beziehung zur Gefassfunktion. *Zentralbl f Herz & Gefasskrankheiten* **12** 295, 1920

6 Kylan, E. Studien uber das Verhalten des Kapillardruckes, insbesondere bei arteriellen Blutdrucksteigerungen. *Zentralbl f inn Med* **41** 368, 1920

7 Danzer, C. S., and Hooker, D. R. Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, *Am J Physiol* **52** 136 (May) 1920

8 Hooker, D. R. Evidence of Functional Activity on the Part of the Capillaries and Venules. *Physiol Rev* **1** 112 (Jan) 1921

In this study we have been particularly interested in the rôle which the capillaries play in the maintenance of the peripheral resistance to the blood stream, and consequently in the etiology of hypertensive states. The problem of hypertension and its relationship to kidney disease still remains unsolved in spite of innumerable searching studies that have been made. Opinion has veered from the extreme view that hypertension is always a result of kidney disease to the opposite extreme that all kidney disease is secondary to hypertension. Both schools still have their advocates. From the maze of facts and theories that have surrounded the subject, one thesis may be granted as established—that the syndrome of hyperpiesia or essential hypertension may exist without any evidence of nephritis. Whether "nephritic hypertension" is a late stage of this or quite a different syndrome is unknown. Blood pressure studies have been singularly unilluminating in clearing up the matter. We have learned to appreciate that brachial blood pressure readings are very variable and that in many instances they depend on the degree of contraction of the arterioles. That the capillaries themselves may be concerned in the maintenance of this pressure was first brought out forcibly by Dale and Cannon, who showed that a paralytic dilatation of the capillaries may cause a great fall in blood pressure, even when the arterioles are contracted. The reverse side of the picture, namely, that the capillaries may themselves be a factor in the maintenance of high arterial pressures, is suggested by some of the studies of Kylin and of Weiss.

Kylin,⁸ using an instrument something like Danzer and Hooker's, has made some very interesting observations on the capillary blood pressure in hypertension and nephritis. His observations are open to question because he used the cessation of the capillary blood flow as the criterion by which he measured the capillary pressure and also because his figures for normal readings are uniformly low—about 10 mm Hg. In glomerular nephritis he found the capillary pressure abnormally high in 100 cases investigated, but in benign nephrosclerosis with hypertension it was always normal. He studied twenty scarlet fever convalescents daily and found in some a marked increase in capillary pressure. In three of these patients a typical glomerular nephritis developed with albumin, casts and red cells in the urine a few days after the capillary pressure had risen. The nephritis set in when the capillary pressure had reached about 23 mm of mercury. The highest capillary pressure obtained ranged from 40 to 55 mm of mercury. In a more recent article,⁹ written in English, he summarizes the results of

9 Kylin, E. Brief Notes on Hypertonia and Kidney Disease. *Acta Med Scandin* 55 368, 1921.

his studies as follows. There are two types of hypertension. The nephrosclerotic hypertension is an arterial, the glomerulonephritic, a capillary hypertension. In the first form the brachial blood pressure is much more labile than in the latter. The hypertension is not the result of the kidney disease, but the glomerulonephritis is a manifestation of a diffuse capillary injury caused by the toxins of certain acute infectious diseases. Some of Weiss'¹⁰ observations seem to confirm these views. He noted an increase in the number and a change in the appearance of the capillaries of the nail-bed in acute, as well as in chronic nephritis. They were longer and more convoluted than normal.¹¹ These observations were confirmed by Thaller and Draga¹² but disputed by Schur.¹³

With these studies in mind we studied a series of patients with hypertension in the wards of the Montefiore Hospital.

We employed the microcapillary tonometer described by Danzer and Hooker⁷ for our determination of the capillary blood pressure. It is the most satisfactory instrument that has been devised for this purpose. In principle it resembles the instrument which Roy and Brown¹⁴ devised in their studies on the capillaries of the frog. Lombard's¹⁵ observation that the human capillaries could be visualized by observing the skin through a microscope after a drop of oil or glycerin had been applied to it was the next step in the development of the technic. Kraus¹⁶ followed this lead and studied the pressure of human capillaries, using a magnification of 10 diameters. It remained for Danzer and Hooker to develop a practical, convenient technic, and to introduce the principle that the cessation of the blood flow in the capillaries, rather than the disappearance of the capillaries marks the proper pressure at which the reading should be taken.¹⁷

10 Weiss E. Beobachtung und microphotographische Darstellung der Hautkapillaren am lebenden Menschen, *Deutsch Arch f klin Med* **119** Heft 1 and 2 1916.

11 Weiss, E. Das Verhalten der Hautkapillaren bei akuter Nephritis, *München med Wchnschr* **63** 925, 1916.

12 Thaller, L, and Draga, E. Zur diagnostischen Verwertbarkeit der mikroskopischen Hautkapillarenuntersuchung am lebenden Menschen, *Wien klin Woch* **30** No 22, 1917.

13 Schur H. Mikroskopische Hautstudien am lebenden, *Wien klin Woch* **32** 1201 1919.

14 Roy, C S, and Brown, J G. The Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, *J Physiol* **2** 323, 1879.

15 Lombard W P. The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, *Am J Physiol* **29** 335, 1912.

16 Kraus. Der Kapillardruck, *Sammlung klin Vorträge Inn Med* No 237-239 315, 1914.

17 For a critical survey of methods to determine capillary pressure see *Friedrich's Ztschr f exper Path & Therap* **19** 2, 1917.

We followed the method of Danzer and Hooker, as outlined in their article. All readings were taken with the hand at heart level and the patient in a sitting posture, at a room temperature of 20-25 C. After the first few observations, we did not scrub the skin of the finger before making our readings, for we found it unnecessary and did not wish to introduce a possible complicating factor. Leonard Hill¹⁸ has questioned the accuracy of this method. He states that the true measure of the blood pressure in the capillaries is that pressure which, when applied, will momentarily check the flow of blood in the capillaries, and that the pressure which will completely check the flow is equal to the pressure in the arterioles which supply the area compressed, because of the backing up of pressure in the occluded vessel. This is undoubtedly true. However, we have followed Danzer and Hooker's procedure of taking the reading as one does a blood pressure reading, i. e., noting the point at which the capillary flow returns as the pressure which has stopped the flow is released. With the drop in pressure, the blood first flows sluggishly through the capillaries but suddenly quickens to a rapid stream. This we have taken as the capillary pressure, and to this Hill's objections do not apply. Hill's second objection is that with this method, the pressure factor dependent on the resistance of the skin to compression is not excluded. As a matter of fact by a method of his own he obtains very low readings for capillary pressures from 2 to 5 cm. of water. Our observations seem to indicate that the resistance of the tissues does not appreciably modify the reading. We have examined many patients who exhibited marked atrophy of the skin in the area studied, as well as many whose skin was normal and others with quite a horny epidermis. The readings obtained did not vary according to the condition of the skin. Moreover in several patients with vasomotor disorders of the extremities we obtained a normal reading—about 20 mm. mercury on one day and a very low reading—from 2 to 3 mm. mercury on another day. The latter reading is so low as to practically exclude the resistance of the skin as a factor.

It is well known that venous stasis will induce an elevation of the capillary pressure. We were careful therefore to exclude this factor in the cases studied. The observations detailed in the following table were made on patients whose systolic pressure was 180 mm. Hg or over, selected at random in the wards of the Montefiore Hospital. For five of the cases we are indebted to the courtesy of Dr. H. J. Wiener who permitted us to examine them in his Metabolism Division of the Vanderbilt Clinic.

¹⁸ Hill L. The Capillary Blood Pressure. *J. Physiol.* **54** 1920. *ibid.* **54** xciii 1921. Hill L. and McQueen J. M. The Measurement of the Capillary Blood Pressure in Man. *Brit. J. Exper. Path.* **2** 1 1921.

TABLE 1—RESULTS OF EXAMINATION OF TWENTY-FIVE CASES

Number	Sex	Age	Diagnosis	Clinical facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg per 100 Cc	Blood Pressure	Capillary Pressure	Capillary Appearance
1 (A G)	M	55	Hypertension, chronic lead poisoning?	No hypertrophy of heart, aortic second sound accentuated, thickening and tortuosity of temporals, slight of retinals	1023 Alk No albumin No casts	39.0	Urea N 10.5 Uric A 1.9 Sugar .97	130/90-95	R 1 27.0 25.0 30.0 23.5 31.0 27.0 24.0 29.0 40.0 L 3 21.5 23.0 30.0 L 4 33.0 35.0 41.0 34.0 L 5 30.0	More looping of the venous arms than normal in my small fine capillaries with one small fine convolution present
2 (M G)	M	58	Hypertension, chronic nephritis	Cardiac hypertrophy, 2 attacks of hemiplegia headaches, shortness of breath, swelling of eyelids, Wassermann negative	Alb ++ Many casts	32.0 36.0	Urea N 15.0 Uric A 3.1	230/128 235/120	30.0 27.0 27.0 30.0 R 3 43.0 48.0 46.0 27.0 38.0 32.0 L 3 38.0 48.0 L 5 44.0 28.0 27.0 33.0 36.0	Capillaries long few looped
3 (S W)	M	50	Hypertension, chronic nephritis, diabetes	Cardiac hypertrophy, albuminuric retinitis, shortness of breath, swelling of feet, left chest tapped a number of times, bloody fluid withdrawn	Marked trace of albumin Many granular casts	40.0 32.5	Urea N 17.5 5/25/21 8/21/21 10/5/21 Uric A 2.5	244/150	35.0 40.0 53.0 49.0 R 3 85.0 60.0 50.0 R 5 41.0 43.0	Capillaries irregularly convoluted, subpapillary plexus seen

4 (M I)	F	58	Hypertension, chronic nephritis, arteriosclerosis	Cardiac hypertrophy, right hemiplegia, thickened tortuous vessels, Wassermann negative	Alb trace Granular casts	20 0	Urea N Uric A Creat	13 5 1 3 4 2	216/120	L 3 40 0 20 0 38 0 31 0 33 0 38 5 30 0 32 0 49 0 46 0 L 4 40 0 37 0 R 3 11 0 11 0 14 0 12 0 13 0 39 0 83 0 90 0 R-2 65 0 47 0	Left, capillaries very long, in several layers, not tortuous Right (hemiplegic), capillaries long, wider, some wound
5 (Ph D)	M	61	Hypertension, chronic nephritis, arteriosclerosis, emphysema	Cardiac hypertrophy, adv thickening and tortuosity of vessels, Wassermann negative, high blood pressure since October, 1918	Alb and casts	18 0	Urea N Uric A	11 4 5 1	212/110	R 3 40 0 46 5 45 0 37 5 54 5 52 0 36 0 R-4 52 5 R-5 38 0 L-3 36 5 39 0 41 0 31 0 39 0 35 0 L-4 39 0 39 5 40 0 L 2 50 0 47 0 L 5 45 0	Very many convoluted capillaries Long narrow capillaries Capillaries looped, longer than normal, (hemiplegic side) Very many capillaries looped
6 (B H)	F	52	Hypertension, chronic nephritis and auricular fibrillation	Cardiac hypertrophy, attacks of decompensation	Alb and casts	11 0	Urea N Uric A Sugar	12 6 2 1 119	270/110	L 3 66 0 70 0 L 5 70 0 R-4 63 0 18 0	Capillaries are long parallel, regular, venous end thick, many subcapillary plexuses (venous)
16 (M L)	M	39	Hypertension, chronic nephritis	Heart normal, Wassermann negative, high blood pressure since April, 1921	1 012 1 027 Occasional hyaline casts	45 0	Urea N Uric A	23 8 1 95	216/120	24 0 45 0 60 0 22 0 60 0	Very long straight and looped capillaries with engorged venous ends

R, right hand, L, left hand, figures 2 3, etc indicate the finger of the hand Thus R 4 means the fourth finger of the right hand

TABLE 1—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg per 100 Cc	Blood Pressure	Capillary Pressure	Capillary Appearance
17 (C G)	F	70	Hypertension, chronic nephritis	Vertigo, dizziness, headaches past six years slight cardiac hypertrophy, slight accentuated second sound and pulmonary second sound blood pressure 235/140	1.010 (24 hr.) 1.011 Alb 0		N P N 45.5 Urea N 39.0 Uric A 2.8 Creat 1.37	196/120	35.0 45.0 26.0 65.0 60.0 65.0 56.0 42.0 52.0 44.0	Capillaries numerous and tortuous
21 (T W)	M	60	Arteriosclerosis extensive with calcification of small arteries and gangrene of leg	Diabetes (?) headaches and dizziness, cardiac hypertrophy, amputation of left leg one year ago for gangrene, cerebral hemorrhage with high blood pressure four years ago	1.005 1.018 Alb trace No casts Many W B C	26.5	Urea N 9.1 Uric A 3.4 Creat 1.5 Sugar 127.0	164/90	L 4 21.0 35.0 27.0 27.0 25.0 L 5 41.0 29.0 33.0 31.5 29.0 L 2 49.0 40.0 40.0 23.0 R-4 26.5 26.5 R-2 42.0 36.5 36.5	Capillaries long, looped, irregular, in many layers, subcapillary plaques very irregular architecture, streaming at 0 mm, venous end thick
7 (A G)	M	59	Hypertension, diabetes mellitus	Cardiac hypertrophy (slight) mild diabetes, with few symptoms, Wassermann negative	1.015 20 Alb neg Sugar trace No casts	45	Urea N 18.9 Uric A 2.5 Sugar 1.98	174/110	L 5 15.0 16.0 18.0 14.0 14.0 L 4 18.0 21.0 17.5 L 2 16.5 16.5 17.5 L 3 17.5 18.5 14.0 17.0	Capillaries increased, no straight loops, curved but not entwined, venous ends somewhat engorged Very greatly elongated and curved, engorged venous ends Many elongated tortuous capillaries Same

8 (J S)	M	44	Hypertension, arteriosclerosis, emphysema, chronic valvular disease, mitral stenosis	Cardiac hypertrophy, aortic second sound ++, slight sclerosis, temporal artery clubbed fingers Wassermann negative	1014 20 Alb 0 to V F T No casts	30	Urea N Uric A	15.4 1.7	164/94	R-5 150 120 140 165 R-4 220 270 190 900 160 R-2 220 130 160	Tortuous and elongated Massive capillaries, some tremendously engorged Many large and small capillaries, normal in appearance Very many capillaries to field
9 (I R)	F	69	Hypertension, general arteriosclerosis, auricular fibrillation	No cardiac hypertrophy, amputated left foot for gangrene blood pressure 170 on admission	No albumin or casts	4 32.5	Urea N Uric A Sugar	14.7 1.3 62	145/90	100 50	Very many capillaries, most in long loops, few with convolutions, streaming at 0, subcapillary plexus visible
10 (P K)	F	60	Hypertension, arteriosclerosis	Cardiac hypertrophy, slight thickening of radials, left hemiplegia three years ago, Wassermann negative	Alb ++ R B C No casts (cystitis)	9/9/21 12.5 10/22/21 20.0	Urea N	11.9	175/85	R-4 50 R-3 70	Capillaries looped, irregularly arranged Hemiplegic hand not examined
11 (B S)	F	55	Hypertension, arteriosclerosis	Cardiac hypertrophy, left hemiplegia three years ago, Wassermann negative blood pressure 250/120 one vein ago, second stroke with death necropsy	1010 1016 Alb, faint trace No casts	25.0	Urea N	27.3	180/95	R-3 150 170 150 120 R-4 90 70 R-2 11.5 7.5 9/16/21 L-5 20.0 20.0 17.0 15.0 14.0 L-2 73.0 68.0 67.0 66.0 62.0 56.0 47.0 37.0 6.0 24.0	Capillaries long, irregular, tortuous, "granular", streaming at 0 extensive subcapillary plexus with capillaries running into it Almost normal looking
12 (P F)	M	66	Hypertension, arteriosclerosis, emphysema	Slight cardiac hypertrophy, sclerosed arteries, clubbed fingers, Wassermann ±	1011-22 Alb ++ Sugar ++ No casts	17.5	Urea N Uric A Sugar	10.8 2.8 101.0	180/100		Extremely convoluted great number flowing at 75 flow visible at 0 streaming both "granular" and rapid

TABLE 1—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg per 100 Cc	Blood Pressure	Capillary Pressure	Capillary Appearance
12 (P F) (Continued)								158/85	10/10/21 L 2 16 0 14 0 10 0 L 5 13 0 11 0 10 0 20 0 18 0 11 0 R-4 20 0 R-5 6 0 R-2 12 0	Some capillaries very large, many convoluted many times, irregular in arrangement, subpapillary plexus visible
13 (B P)	F	63	Hypertension, emphysema, diabetes mellitus	Moderately enlarged heart, aortic second sound ++ in microscopic cap pulse, both legs amputated for diabetic gangrene 5 years ago, (X ray calcified arteries), Heberden's nodes on all fingers, blood pressure, 180/146 in 1919, 186/80 in 1921, Wassermann negative	1011 1 022 Alb ++ Sugar ++ Hyalin and granular casts	7 5	3/3/21 Urea N 15 7 Sugar 130 10/10/21 Urea N 36 6 Sugar 152 0 12/7/21 Urea N 22 4 Sugar 122 0	198/80 210/85	R 3 26 0 27 0 22 0 35 0 R 1 13 0 15 0 R-3 21 0 R 2 23 0 21 5 10 0 14 0 11 0 L 4 14 5 11 5 L 3 17 0	Very many small fine capillaries Longer and more tortuous than normal Very long capillaries, subpapillary plexus visible
14 (M G)	F	47	Hypertension, chronic nephritis (?)	Cardiac hypertrophy, aortic second sound greater than pulmonary second sound, systolic at apex and base, blood pressure 220/120, Wassermann negative	10/10/13 Alb ++	63 1 hr (in travenous)	N P N 38 6 Urea N 29 4 Uric A 3 6	204/140	L 3 11 0 6 0 19 0 7 0 11 0 29 0 25 0 13 0 L 2 17 0 23 0 21 0 22 0 13 0 16 5 L-4 36 0 28 5	Long, somewhat convoluted Capillaries very long, extremely looped Very long, looped Very long and convoluted, few loops

15 (N D)	F	50	Hypertension	Cardiac hypertrophy, aortic second sound +- greater than pulmonary second sound, blood pressure 235/120 to 190/100, normal irides, normal eye-grounds	1 011 20 Alb 0 to V F T No casts Sugar +	73	Urea N Creat Sugar	77 09 94	208/100		270 100 250 175 L 2 290 290 170 L 3 100 R 3 300 320 260 R 4 220 160 150 130 60 150 170 110 100 130 75 170 70 70 80 70	Massive capillaries with many convolutions Very wide and long Very long, no loops Capillaries numerous, long, several layers deep, moderately tortuous
18 (S S)	M	62	Hypertension asthma, chronic bronchitis, myocardial degeneration	"Asthmatic attacks", no enlargement of heart, headaches, secondary anemia	1 010 14 No alb or casts	475	Urea N Uric A	194 39	174/72	R 4 110 40	Capillaries extremely long, crowded together with many convolutions, granular streaming in most at 0, great number of anastomoses	
19 (F G)	F	48	Hypertension, chronic nephritis, uremia	Persistent vomiting, loss of weight and strength, headaches cardiac hypertrophy, secondary anemia, Wassermann +- ±	1 007 1 030 Alb marked trace Rare gr casts W B C Some R B C	6	10/26 Urea N Uric A Creat 10/31 Urea N Uric A 11/11 Urea N Uric A	1260 94 74 1120 116 1100 71	195/104	R 3 50 50 R 2 100 9/19/21 L 3 315 170 195 120 230 R 4 225 180	Capillaries very long no loops flowing at 0 with granular streaming Capillaries long many with one or more loops, quite irregular some capillaries very thick	
20 (S S)	M	55	Hypertension, cardiac hypertrophy, emphysema, chronic nephritis	Edema of legs, dyspnea, abdominal distention Wassermann negative	1 024 1 011 Alb trace Hyalin and granular casts	40	Urea N	230	226/100			

TABLE 1—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry Mg per 100 Cc	Blood Pressure	Capillary Pressure	Capillary Appearance	
20 (S S) (Continued)									18 0 15 5 19 5 22 5 R-5 17 0 20 5 23 5 13 0 R 2 38 0 25 0 26 0 10/13/21 R 4 28 5 21 0 25 0 23 0 L 3 26 0 29 0 25 0 L-4 34 0 27 0 21 0 38 0		
22 (G F)	M	68	Hypertension, chronic nephritis, emphysema	Cardiac hypertrophy aortic second sound +, old left hemiplegia blood pressure 260/140 to 210/120, no cardiac symptoms	1 016 1 017 Alb trace Few hyaline casts	Less than 5	Urea N 17.6 Uric A 1.6	210/120	R 3 26 0 20 0 L 4 11 0 4 0 0 0	Capillaries long, many convoluted, no flow in 0 mm in many capillaries, many rows of capillaries visible	
23 (B F)	F	45	Hypertension, general arterio sclerosis, chronic nephritis	Left hemiplegia three years, headaches, cardiac hypertrophy, aortic second sound + old hemorrhages in fundi	1 008 Alb ++ Few granular casts	21	Urea N 14.1	238/133	R-4 24 0 24 0 19 0 R-5 23 5 16 5 20 0 19 0	Capillaries very long and thin, very many to field, no convolutions, subcapillary plexus visible	

Danzei and Hooker determined that the normal capillary pressure ranged from 18 to 22 mm of mercury. They found that in any individual most of the readings on different capillaries varied from 6 to 7 mm of mercury, although in many capillaries the difference was greater. They, however, discarded the very high and the very low readings and took as the capillary blood pressure the average of those which did not exceed this variability. We, too, as is apparent from

TABLE 2—SHOWING THE DISTRIBUTION OF THE READINGS OF CAPILLARY PRESSURE¹

Case	Mm Mercury								
	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Patients With Hypertension									
1			11	5	1				
2			7	6	5				
3				2	4	2			1
4		6	1	9	3		1		2
5				13	6	3			
6					1		1		
16			2		1	2			
17			1	1	3	3	2		
21									
7		23	4						
8	5								
9	3								
10	2								
11	3	5							
12a	4	2	1	1	1	4	14		
12b	3	9							
13	1	7	6	1					
14	6	15	13	2					
15	5	2							
18	1	1							
19	3								
20a		9	7	2					
20b			9	2					
22	2	2	1						
23		4	3						
Patients With Normal Blood Pressure									
24		7	12	1	1				
25		21	20						
26			18	1					
27		11	9	3	1				
28	11								
29	1	8	4						
30	3	11	1						
31		3							
32	6	15	5	3					
33	3	12	5						
34			3						
35			2	2	1				

* Cases in which only very few readings are recorded are ones in which all of the capillaries in the microscopic field exhibited a reappearance of the blood flow at the same pressure. Early in the work the number of capillaries observed were not counted.

Table 1, encountered wide differences between the pressure readings in different capillaries of the same individual. This variability is so constant in most cases that we feel it cannot be ignored. It has long been known that there is a great variation in the degree of filling of different capillaries and in the rate of their blood flow. Roy and Brown drew attention to this in 1879 and many others have subsequently noted the same phenomenon. It remained for Kiøgh to point out the relationship of this variability of flow to the functional needs of the

tissues With the inconstancy of flow there must be a corresponding fluctuation of the capillary pressure Thus the variations in the readings which we observe are of real significance and should be recorded We deem it wisest to record all of the observations Because of the wide range of variability and the relatively small number of readings, an average would be deceptive It is possible that the degree of variability of the readings in different individuals may have some clinical significance That it is not due to errors of measurements is shown by the fact that successive readings on one capillary taken at the same sitting are usually quite constant

It has been suggested that high readings are due to the fact that the capillaries on which such pressures are observed are seated more deeply in the tissues, or that some anatomic peculiarity is the determining factor The following facts show that this does not usually obtain By careful focussing of the microscope one can show that the capillaries giving high readings are often superficial The size of the capillary bears no relationship to the pressure observed therein Moreover, if the same group of capillaries is kept under observation for a period of time, or is studied on different days, marked variations in their pressure are observed For instance, in Case 6 a group of four capillaries of varying shapes and sizes gave the following successive readings, the figures for all four capillaries at any one time being the same—45, 38, 52 Four days later the readings were 48, 49, 49, 55 On both days during the period of observation one of the four capillaries disappeared from view for several minutes at a time On such occasions we were able to make it reappear by raising the pressure to 90 or 100 and quickly releasing it several times in succession This acts, we believe, as a mechanical stimulus to the arterioles, capillaries and venules In another patient (Case 26) the following note was made

While the pressure in most of the capillaries in the microscopic field was 28, in one capillary there was but the slightest streaming of blood at 0 The pressure was raised to 90 and quickly released Thereupon the microscopic field became markedly hyperemic and the pressure in most of the capillaries was 25 In the capillary in which the reading had been 0, the pressure now was 12

We think that at times unlike pressures in different groups of capillaries are due to the fact that the arterioles supplying the groups exhibit different pressures or degrees of contraction Case 25 may be cited as an example Observations made on the fourth finger of the left hand passing from the left to the right side of the nail-bed, so that the first and last readings were made on capillaries separated by a distance of one centimeter, were as follows

Left 8, 8.5, 10, 15, 20 Right
and again Left 10, 10, 14, 15.5, 17, 20 Right

It is clear from this discussion that the capillary pressure in the same and different vessels may vary from physiologic as well as from anatomic causes

It is difficult to draw any final conclusions from a study of the tables. The cases fall into two groups—those with high capillary pressure and those with a low or normal capillary pressure. It is impossible to classify the patients clinically. Neither the history, the physical examination, nor the study of kidney function reveals any differential features. Similar urinary findings are common to both groups, in both we find low as well as normal phenolsulphonephthalein excretion. There is no difference in the pulse pressures in the two series. While it is true that on the average patients with a high capillary pressure exhibit a high diastolic blood pressure, there are sufficient exceptions to this rule to invalidate any supposition of a causal relationship between the two.

On further reflection these apparently vicarious figures find some theoretical justification. If Kylin's division of hypertensive states is a correct one, it may well be that those of our patients who showed kidney involvement with a low capillary pressure did not fall within the group exhibiting glomerulonephritis and general capillary disease. As a matter of fact necropsies in two of our cases support this belief. The following extracts from the autopsy protocols of Cases 11 and 19 give no evidence of a diffuse glomerulonephritis.

REPORT OF NECROPSY FINDINGS

CASE 11—Right kidney weighs 120 gm, left, 80 gm. Capsule markedly adherent. Scattered large arteriosclerotic scars. On section the cortex varies in thickness, striations irregular, vessels prominent.

Microscopic examination reveals scarring with thickening and obliteration of the vessels in the depressed areas. Slight fibrosis of the glomeruli with some thickening of Bowman's capsule. In the scarred areas the glomeruli are fibrosed.

There is marked arteriosclerosis of the aorta, of the cerebral and coronary arteries. In the posterior wall of the left ventricle there is a large white scar. There is a large cystic area in the right occipitoparietal region, and a hemorrhage in the left internal capsule.

CASE 19—Each kidney weighs 50 gm. They are firmer than normal. Capsule adherent, leaving on removal a finely granular surface. The cut surface is pale and granular. The cortex is from 2 to 3 mm in diameter. Striations are absent. Small vessels are prominent.

Microscopic examination shows a complete loss of normal architecture. Marked sclerosis of the larger vessels. Tubules are arranged in irregular groups and are dilated. Their cells are low, cuboidal, and the lumen is filled with exudate. There is a great deal of connective tissue with round cell infiltration. Most of the glomeruli have undergone a fibrous or hyaline change. A few still have a normal appearance, but even in these Bowman's capsule is much thickened.

Diagnosis. Primary contracted kidney.

When we recall that experienced clinicians have recognized the impossibility of diagnosing the anatomic lesion in the kidney from the clinical picture, particularly in chronic nephritis, we are in a position to understand why, in the cases we studied, we have been unable to predict which cases will exhibit a high capillary pressure as one of the manifestations of a glomerulonephritis. If our postulates hold true, however, and for confirmation we must await the postmortem examinations on appropriate cases, the estimation of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis, from other types of kidney disease. It is not, however, of value in the differentiation of nephritic from essential hypertension.

Another question which remains unsolved is whether the capillary hypertension contributes to the general arterial hypertension, or whether it is a concomitant phenomenon. It is well known that when, in patients with hypertension, particularly, serial blood pressure readings are taken, the final reading will often be considerably lower than the first one. Table 3 presents such a series of readings on the two groups of patients.

TABLE 3

High Capillary Pressure	Blood Pressure in Mm. Hg					Length of Observation, Mn	Drop in Systolic Blood Pressure, Mm. Hg
Case 2	240/120	230/110	220/100	206/100	206/100	5	34
Case 3	206/120	204/120	200/120	202/120	200/110	10	6
Case 5	250/140	240/150	228/125	214/125	212/122	12	38
Low Capil- lary Pressure							
Case 7	180/110	184/103	184/110	180/110	180/110	10	0
Case 12	184/102	176/ 96	174/ 96	180/ 94	178/ 96	12	6
Case 8							
10/ 8/21	186/ 90	174/ 90	170/ 80	168/ 80	160/ 90	10	26
10/10/21	152/ 82	160/ 90	154/ 86	158/ 88	156/ 88	10	4
12/ 1/21	184/100	180/ 90	166/ 90	176/ 96	174/ 94	10	10
12/ 6/21	174/ 96	172/ 94	170/ 90	174/ 90	172/ 90	10	2

It is apparent that the blood pressure is equally unstable in both groups. Were the high capillary pressure a cause for the sustained hypertension, one might imagine that in such cases the blood pressure readings would be more constant.

Furthermore, were the connection a close one, one would expect the blood pressure to vary, *pari passu*, with the capillary pressure. We have observed this only in Case 12, where readings taken on different days at different levels of blood pressure revealed parallel changes in the capillary pressure. We must dispute the statement of Secher¹⁹ that the capillary pressure, as a rule, follows the blood pressure. He cites one case in which wide fluctuations of the blood pressure were accompanied by parallel changes in the capillary pressure.

¹⁹ Secher K. Kliniske Kapillaerundersøgelser, Ugeskrift f. Læger **83** 899, 1921.

The mechanism of a low capillary pressure is easily explained. A constriction of any blood vessel will be followed by a rise of pressure central to the constriction, and by a fall of pressure peripheral thereto. In hypertension, due to a contraction or a diminution of the lumen of the arterioles, the capillary pressure will be low. Thus it would seem that in most of our cases of hypertension there is a narrowing of the arterioles. A high capillary pressure will follow a dilatation of the arterioles or a constriction of the venules, or a high venous pressure due to stasis. It is not clear how disease of the capillaries themselves would lead to a high capillary pressure, particularly when we recall that arteriosclerosis of itself does not lead to a high arterial pressure. This is the weak point in Kylin's theory. It is conceivable that a lesion of the venous loop of the capillary might raise the pressure in the arterial loop, or that a stiffening of the endothelial tube due to disease might increase the pressure needed to check the blood flow in the capillaries.

That the appearance of the capillaries in our cases does not correspond to the accepted normal is evident from the table. We are not ready, however, to subscribe to Weiss' positive views as to the significance of these morphologic changes. We believe that the normal has not yet been sufficiently established. We have observed in normal individuals capillary pictures that correspond to descriptions of the capillaries characteristic of nephritis and arteriosclerosis. In general, it may be said, however, that the capillaries when diseased behave as do the arteries. They become long and, as a consequence, tortuous. This may be due to an organic change in the capillary or it may be as Lapinsky²⁰ pointed out, due to loss of tone following injury to the nerve supplying the area in question.

CONCLUSIONS

1 In patients with normal blood pressures the blood pressure in the capillaries of the fingers rarely exceeds 30 mm of mercury.

2 Patients with hypertension fall within two groups that cannot be differentiated clinically. In the first group the capillary pressure ranges between 21 and 70 mm of mercury, rarely higher and only very exceptionally lower. Most of the readings fall between 30 and 60. In the second group the capillary pressure falls within the range of normal, with a tendency to be low rather than high.

3 It is possible that patients who exhibit high capillary pressures are suffering from a general capillary disease with a glomerulonephritis as one of the manifestations. If this view is confirmed, the estimation

²⁰ Lapinsky, M. Studien über die lokale Blutcirculation im Bereiche gelahmter Nerven, *Arch f Anat & Physiol (Physiol Abtheil)* 477, 1899 Supplement.

of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis from other forms of kidney disease

4 In essential hypertension the capillary pressure is low

5 In any given individual varying pressures are usually observed in different capillaries In patients with a normal capillary pressure the difference between the high and low readings is on the average 18 mm Hg In patients with a high capillary pressure this difference is on the average 36.6 mm Hg Thus the variability of the capillary pressure is greater in patients with high readings

6 The variability of the capillary pressure depends on physiologic as well as on anatomic moments

7 Mechanical stimulation of the capillaries will alter the blood flow, as well as the blood pressure within the capillaries

AN ELECTROCARDIOGRAPHIC STUDY OF FIFTY PATIENTS DURING OPERATION^{*}

W G LENNOX, M D

PI KING, CHINA

R C GRAVES, M D, AND S A LEVINL, M D

BOSTON

For a thorough understanding of the action of the heart, it is important that it be studied under various conditions of stress. This investigation was undertaken to determine whether there are any abnormalities in the mechanism of the heart beat, demonstrable by electrocardiography, during the period of anesthetization and surgical operation.

Heard and Strauss¹ reported a case of atrioventricular rhythm detected electrocardiographically in a patient still under ether following an operation. They state, "no other cases of nodal rhythm have been observed by us in a series of twenty-one cases in which electrocardiographic records have been taken during anesthesia." Levine² reported cases of acute cardiac upsets occurring in association with surgical operations. In two of his cases electrocardiographic tracings were made during attacks of paroxysmal auricular tachycardia while the patients were still under ether. These two reports were the only references to the subject found in the literature.

MATERIAL AND METHODS

This paper covers the study of fifty operations performed on forty-eight individuals on the surgical service of the Peter Bent Brigham Hospital during May and June, 1921. The cases were selected to the extent that the widest possible variety of conditions of age, type of anesthesia, cardiac condition, operative procedure, etc., were covered. They represent the more serious of the usual operative cases. The total time during which patients were under observation was seventy-five hours. During this period a total of 1,750 records were made. Electrodes of the type described by Cohn³ were applied and preliminary tracings made before the beginning of anesthesia. By

* From the medical and surgical clinics of the Peter Bent Brigham Hospital.

1 Heard, J D, and Strauss, A E. An Electrocardiographic Study of Two Cases of Nodal Rhythm Exhibiting R-P Intervals, *Am J M Sc* **75** 238, 1918.

2 Levine, S A. Acute Cardiac Upsets Occurring During or Following Surgical Operations, *J A M A* **75** 796 (Sept 18) 1920.

3 Cohn, A E. A New Electrode for Use in Clinical Electrocardiography, *Arch Int Med* **26** 105 (July) 1920.

means of an electric buzzer the anesthetist signaled to the electrocardiograph operator the moment at which anesthesia and operation were begun and ended, and also indicated any critical stages in the operation or in the patient's condition. By this means, tracings and operative procedures were correlated. Short records were made at intervals from the beginning of anesthesia until the time when the patient was ready to leave the operating table. On the average a tracing was made every two and one-half minutes. Graphic records were obtained for about 3 per cent of the time the patients were on the table. The galvanometer string was watched for a much longer period than this, and any gross abnormality of rate or rhythm, lasting more than a few minutes, would have been detected. Most records were of Lead II, but occasionally, because of manipulations during operation in abdominal cases, it was necessary to use Lead I.

HEART RATES

The rate of the heart during operation is a matter of practical importance. Operators usually rely on the pulse rate as furnished by the anesthetist. In this study it was found that the heart rate, calculated from electrocardiographic tracings, in many instances was much higher than the count the anesthetist reported. The highest heart rate in this series was 217 beats per minute, occurring during the etherization of a child. The highest recorded pulse rate in this case was 180. In seventeen cases, or 34 per cent, the heart rate was twenty or more beats per minute faster than the highest recorded pulse rate. In nine cases, or 18 per cent, this discrepancy amounted to thirty or more beats. The most marked difference was in the case of a girl, who held her breath during the early stages of etherization. Her heart and pulse rates are shown in Figure 1. Discrepancies occurred with equal frequency under ether and gas-oxygen anesthesia. In certain of these cases there may have been an actual pulse deficit. In others the discrepancy might be explained by the fact that the pulse rates taken at five minute intervals did not catch short rises in rate shown by the more frequent electrocardiographic readings. Again, the highest rates and the most marked discrepancies occurred usually during the induction of anesthesia, when the pulse rate was taken by a nurse from the ward. During the period of operation, a trained anesthetist took the readings, using the temporal artery.

These observations show that the anesthetist's chart of pulse rate cannot be taken in many instances, as a record of heart rate. For those cases in which it is important that the operators have accurate information, the rate should be obtained from the apex beat. This is easily done by strapping a stethoscope over the precordium, using tubing of sufficient length to reach the anesthetist. Another accurate method,

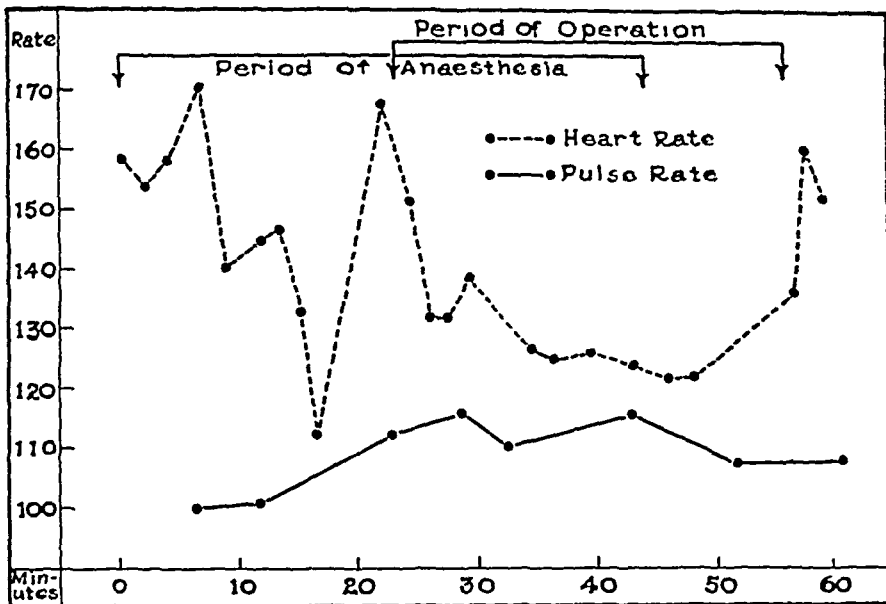


Fig 1—Upper line shows the heart rate as determined from electrocardiograms, lower line, the pulse rate as recorded by the anesthetist

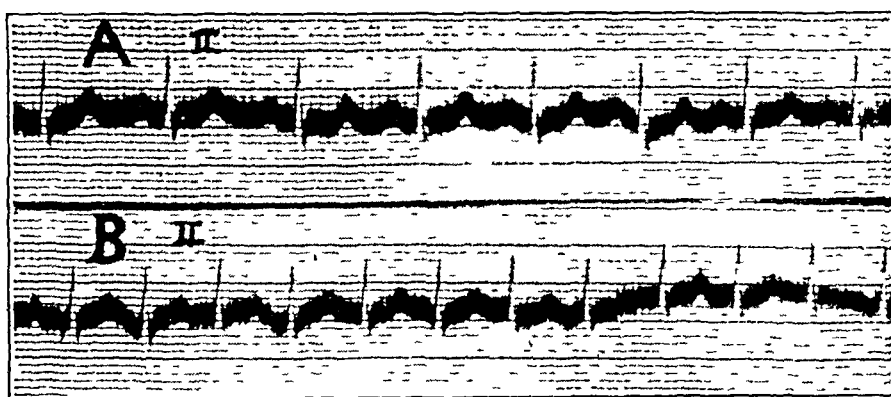


Fig 2—Case 7 Operation, fixation of uterus A Tracing taken twenty-six minutes after beginning of operation, rate 104, rhythm normal B Taken four minutes later than A, rate 164, paroxysmal tachycardia

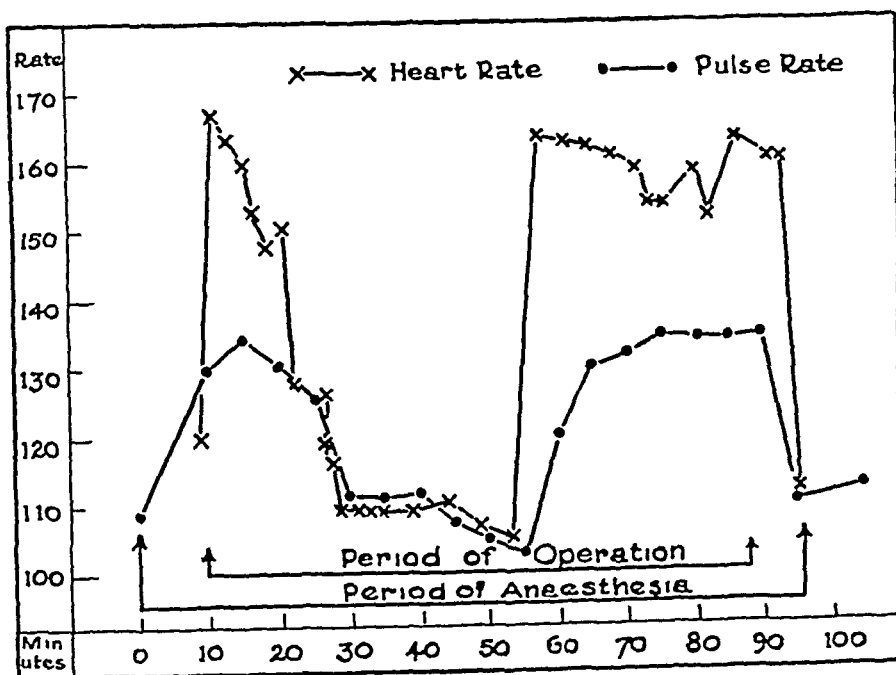


Fig 3—An instance of paroxysmal tachycardia unsuspected by the operating staff

used in the head operations of this series, is to count the pulsations in the brachial artery as heard in the auscultatory method of obtaining blood pressure records

ABNORMALITIES OF RHYTHM

Paroxysmal Tachycardia—One patient, a woman, 80 years of age, showed this type of arrhythmia. The electrocardiogram appears in Figure 2, and the heart and pulse rates in Figure 3. The first sharp rise in rate, from 120 to 167, occurred during the half minute or so required to change from one lead to another. Without the electrocardiograph, this abnormality would have gone unrecognized, for the anesthetist noted only a rise of pulse rate to 135. The fast rate was unaccompanied by any adverse change in the patient's condition.

Premature Beats—In eleven cases, premature beats were recorded. They were ventricular in origin in seven cases, and auricular in four. It should be stated, however, that two of the eleven showed premature beats in the preliminary tracings and in another there was a clear past history of premature systoles. One case which showed paroxysmal auricular tachycardia and premature beats on entrance to the hospital, ten days before operation, showed no abnormality during operation. During the ten day interval he had been on digitalis. The records of eight of the eleven cases showed only one or two premature beats. In two cases, premature beats occurred for short periods as often as every third beat. In none did the anesthetist note the irregularity. The time relations of the premature beats to the operation are shown in the upper part of Figure 4.

Sinus Arrhythmia—The occurrence of well marked sinus arrhythmia was noted in three cases.

DISTURBANCES IN CONDUCTION

Delayed auriculoventricular conduction, with a lengthening of the P-R interval from 0.2 to 0.24 second, occurred in one patient during an operation for the ligation of a thyroid artery. Krumbhaar⁴ reported forty-seven cases of toxic goiter in which tracings were taken before and after operation, two of these showed a delay in conduction time after operation. In regard to disturbances in the branches of the conduction apparatus, it is worthy of note that in our series, no case showed a prolongation of the QRS interval. One case showed a widened QRS complex (0.1 second) in the preliminary tracing, but it did not increase during the operation. The patient died eight days later from bronchopneumonia and pulmonary embolism.

⁴ Krumbhaar, E. B. *Electrocardiographic Observations in Toxic Goiter*, *Am J M Sc* 155:175, 1918.

There was no evidence of heart failure, but at the necropsy an area of fibrous myocarditis 1×2 cm in size was found in the wall of the left ventricle

DISLOCATION OF THE PACEMAKER

The chief interest of the study was found to lie in the frequent displacement of the cardiac pacemaker, as evidenced by changes in the shape, direction and position of the P wave (auricular complex) Fifteen of the cases, or 30 per cent, showed some variation in the

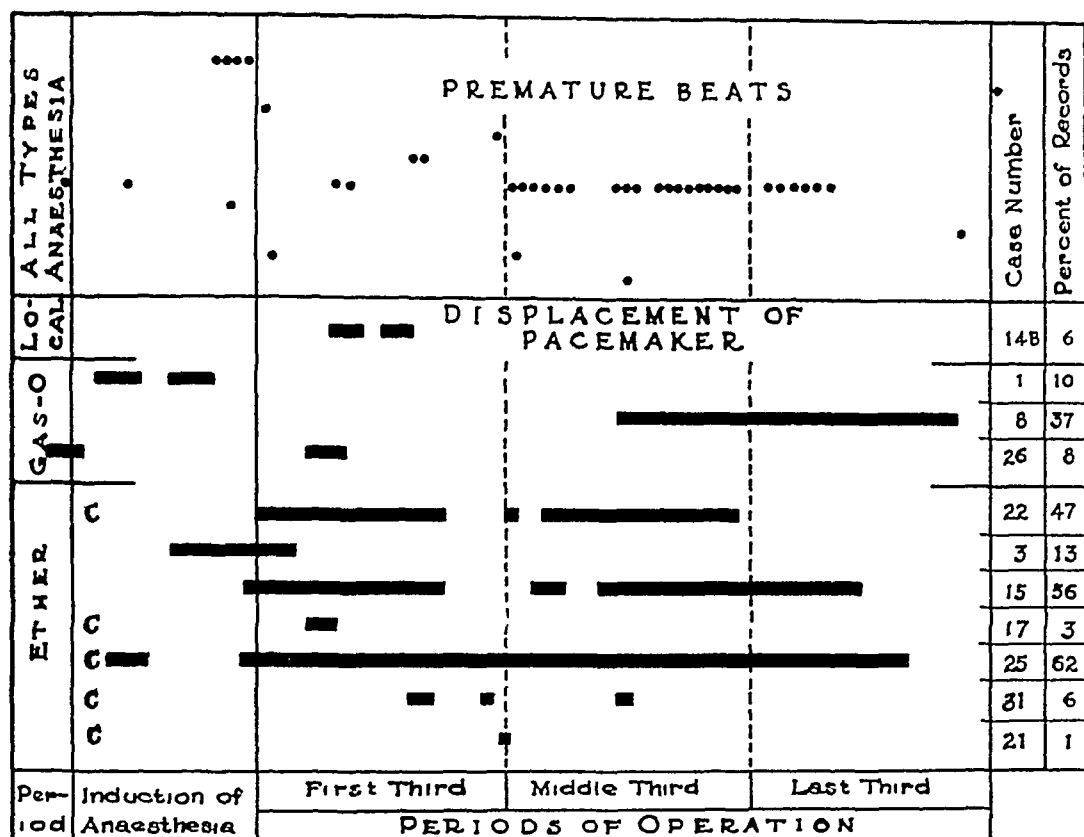


Fig 4—The chart illustrates the period during which premature beats and displacement of the pacemaker occurred. The upper portion is for the ten cases which showed premature beats. Each dot represents one such beat. The lower portion is for the eleven cases which showed marked abnormalities of the P waves. They are grouped according to the anesthetic used. In the ether group the letter C indicates those receiving ether by the Connell apparatus. On the right the first column of figures gives the case number and the second column the percentage of records which showed the abnormal rhythm. The length of the black line is, in each case, a rough measure of the percentage of records which showed the abnormality.

P wave not present in the preliminary tracings. In three of the cases the abnormality consisted only in a shortening of the P-R interval of 0.04 second or more. This shortening was not due to an increase in rate. In one of the cases there was only a flattening of the P waves. Various explanations for such flattening have been discussed by Wil-

son,⁵ e g, diminution in contractility of auricles, interference of two rhythms, changes in the path of the contraction wave over the auricles and changes in the location of the pacemaker. In the remaining eleven cases the tracings showed more marked variations of the auricular

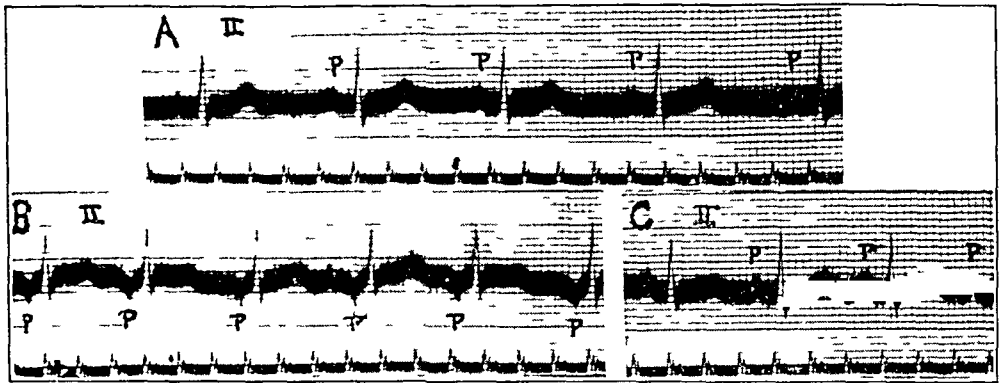


Fig 5—Case 17 Operation, tonsillectomy. Lead II. A Normal tracing, rate 68. P-R interval 0.16 sec. Taken at signal for first incision. B Inverted P waves, rate 94. P-R interval 0.12 sec. Taken two minutes after A. C Normal tracing, rate 59. Taken one minute after B.

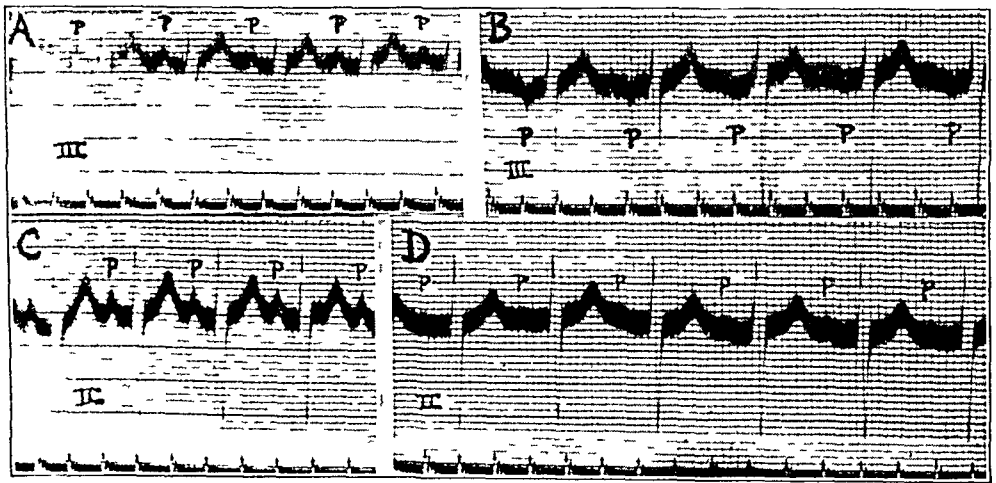


Fig 6—Case 21 Operation avulsion trigeminal ganglion. A Lead III, normal tracing, rate 121. P-R interval 0.16 sec. B Lead III inverted P waves, P-R interval 0.12-0.16 sec. rate 101. C Lead II normal tracing, rate 140. D Lead II P waves greatly flattened, rate 107. Taken two minutes previous to C.

complex, i e either an absence of the wave, or an inverted P wave with diminished P-R interval, or even the P wave following the R wave, producing an R-P interval.

5 Wilson F N. Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated with Respiration, *Arch Int Med* 16:86 (July) 1915.

Following the classification used by Wilson⁶ in reporting his cases of A-V rhythm which resulted from the injection of atropin, these eleven cases are divided into three groups

1 *Cases in Which the "P" Wave Is Inverted and the P-R Interval Reduced*—Three of the patients showed this abnormality. In Figure 5, three successive records are shown. The first was taken on the signal denoting the beginning of operation (tonsillectomy), the second, which shows inverted P waves, two minutes later, and the last one minute after the second. The rate of the heart in the middle (abnormal) record is intermediate between the rates of the other two. Figure 6, from another case, is of interest in that it shows in one lead at one time an inverted "P," and in another lead at another time a markedly flattened "P."

2 *Cases in Which the "P" Wave Is Absent*—Seven of the cases showed a disappearance of the P wave. Examples from three of these are shown in Figures 7, 8 and 9. In Figures 7 and 8 there is in some of the cycles a slight irregularity of the auricular complex, suggesting an interference of two rhythms. In some instances interpretation was difficult because of the artefacts produced by the operative procedures. Figure 8 is of particular interest for it shows the onset of the abnormal rhythm. Here the transition occurs abruptly, without preliminary shortening of the P-R interval, but with slight slowing of the rate. In Figure 9 (C) a condition of auriculoventricular dissociation probably exists, the auricle responding to the sinoauricular node and the ventricle to the auriculoventricular node. In two of the seven cases, in addition to records showing absent P waves, there are other records showing inverted P waves.

3 *Cases in Which the "P" Wave Is Inverted and There Is an R-P Interval*—One case belonged to this group. Figure 10 (B) shows the established abnormal rhythm with the heart responding to but one pacemaker. Figure 11 from the same case shows the onset of abnormal rhythm, the P-R interval becoming shorter and shorter until the P wave is lost in the R wave. In this tracing, as in Figure 9 (C), there is a mixed rhythm, the heart responding to two pacemakers. The transition is accompanied by a slight decrease in rate. The operation was the excision of a right cervical rib in a young woman. The operator "neither saw nor touched the vagus nerve."

In addition to the above group of eleven cases, there was one patient whose tracings showed bigeminy and marked differences of the P wave in successive cycles. As his control tracings, both before and after operation, showed the abnormality this case is not included in the

6 Wilson, F. N. The Production of Atrioventricular Rhythm in Man After the Administration of Atropin, *Arch Int Med* 16:994 (Dec) 1915

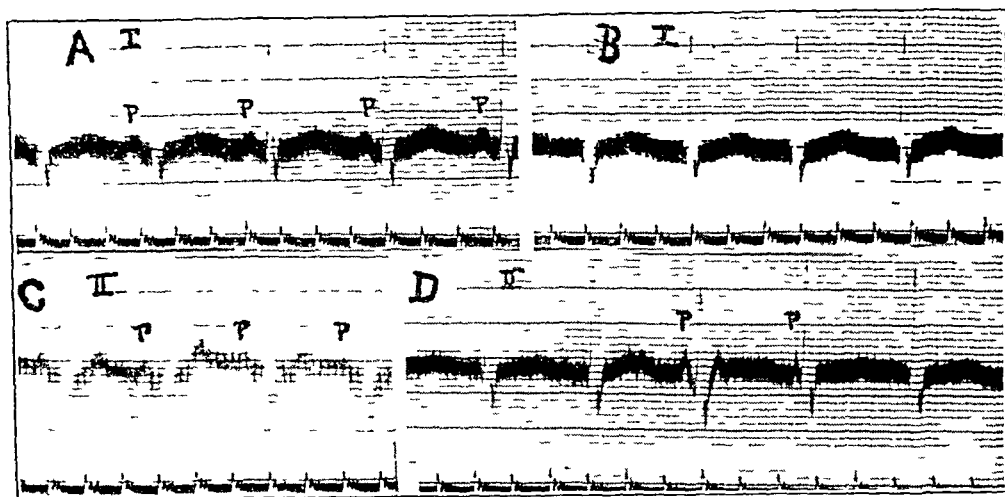


Fig 7—Case 25 Operation, excision tumor of cerebrum A Lead I, normal tracing, rate 93 B Lead I, absent P waves, rate 103 C Lead II, normal tracing, rate 108 Taken seven minutes after beginning of anesthesia D Lead II, P waves are in some cycles absent, in others the P-R interval is much diminished, rate 107

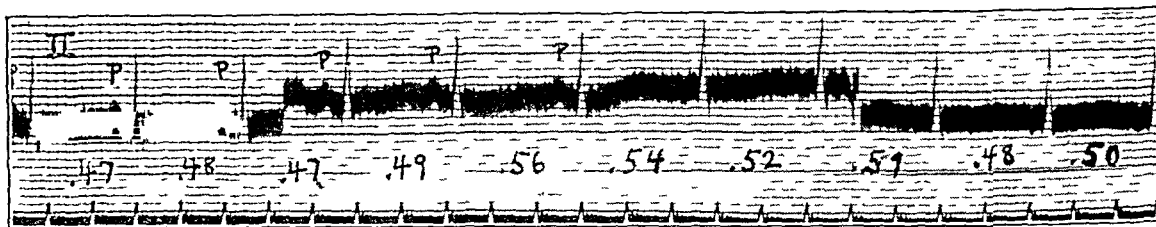


Fig 8—Case 31 Operation, cerebellar exploration Lead II Note disappearance of P waves with slight decrease in heart rate Figures indicate length of heart cycles

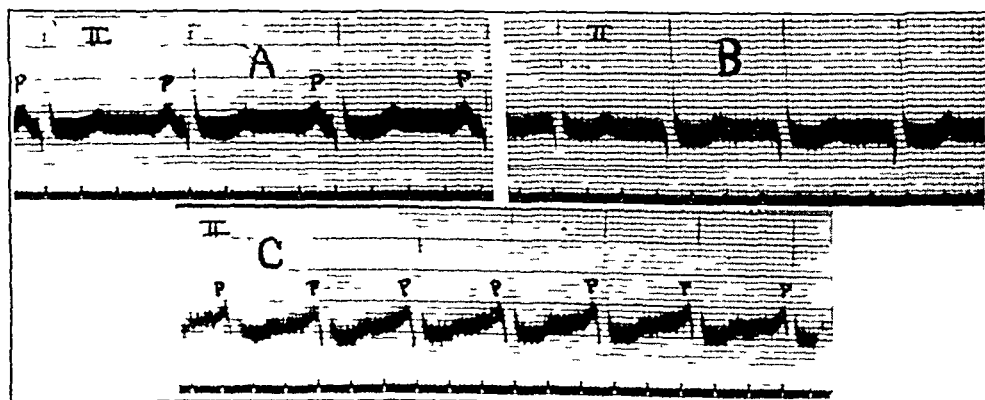


Fig 9—Case 1 Operation, suprapubic prostatectomy Lead II A Normal tracing, rate 74 B Absent P waves, rate 94 Taken three minutes after beginning of anesthesia C P-R interval diminished, P upright, rate 110 Taken three minutes after B

preceding group. One of the eleven cases showed a single record with inverted P waves just before the beginning of anesthesia. Aside from the constantly abnormal case mentioned above, this is the only instance in the series of fifty cases of a disturbance of the pacemaker occurring in any of the control tracings taken before and after operation. In all cases the abnormality had disappeared before the patient left the operating table. Records were taken during convalescence of several

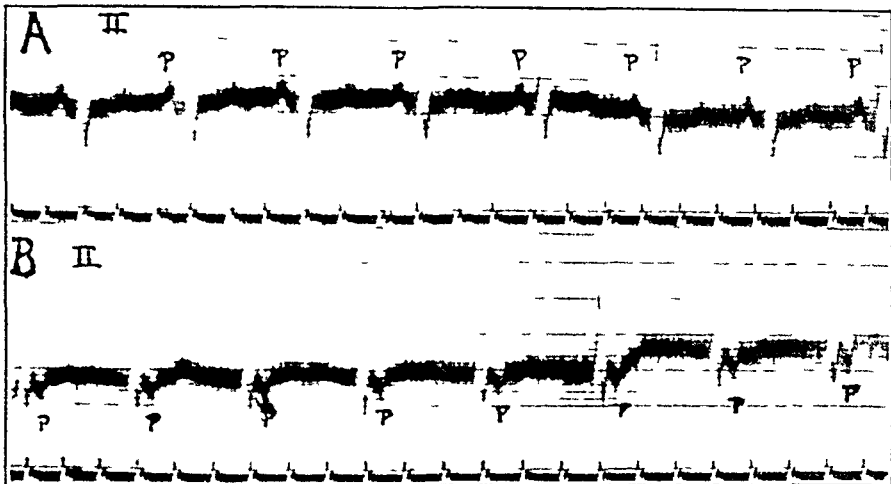


Fig 10—Case 22. Operation, excision cervical rib. Lead II. A Normal tracing, rate 99. Taken at time of first incision. B Inverted P waves, R-P interval of 0.08 sec. rate 99. Taken one minute after A.

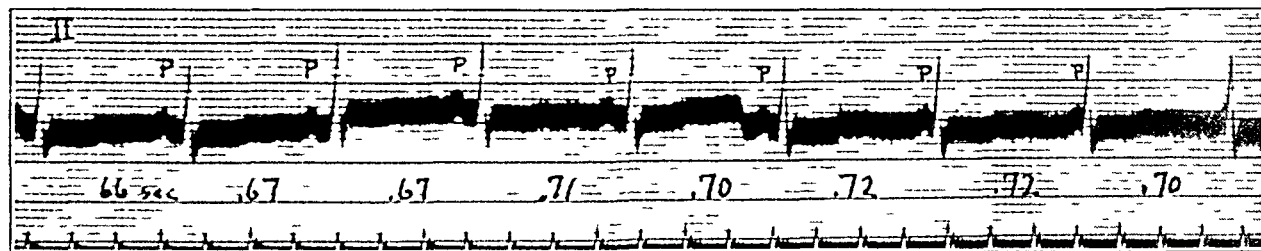


Fig 11—Case 22. Lead II. Onset of abnormal rhythm. P is upright, the P-R interval progressively diminishing, with slight decrease in rate. Figures indicate length of heart cycles.

patients who had shown abnormality of P waves during operation. All were found normal. Two of the fifty cases showed auricular waves which were, in some of the tracings, considerably larger than the normal P waves for those individuals.

Significant variations in the height of the R or T waves, other than a transient inversion of a low T wave in one case, were not noted.

DISCUSSION OF CASES SHOWING A MARKED VARIATION IN THE P WAVES

In the preceding section we have sought to present graphic records of abnormalities rather than their interpretation. The question now

arises as to how many of these are examples of A-V (atrioventricular) rhythm. A large proportion of such cases would not be inconsistent with experimental findings. Levine,⁷ while taking electrocardiographic records of etherized cats, about every six minutes, found that in fourteen out of forty-seven experiments, tracings showed the presence of A-V rhythm. In almost all instances the abnormal rhythm appeared after the etherization of the animal but before the beginning of the experiment (intravenous injection of strophanthin).

There are difficulties, however, in the way of interpreting all these abnormal tracings in the present study as instances of A-V rhythm. In the first place, there is in the literature a lack of unanimity in the definition of this condition. Should the term be confined to those cases of pure A-V rhythm in which the heart is responding to but one pacemaker located in the A-V node, or should it include cases of mixed or double rhythm in which impulses arise from both the S-A (sinoauricular) and A-V nodes? There is a difference of opinion concerning the criteria by which A-V rhythm is to be diagnosed from electrocardiographic tracings. Some writers consider it essential that the P wave be inverted. On the other hand, the statement appears in a recent paper that in A-V rhythm the P wave is frequently though by no means constantly inverted.⁸ Carter and Wedd,⁹ in reporting twelve cases of inverted P in Lead III, consider that a transient inversion of P means a displacement of the pacemaker.

Furthermore, in those cases showing P waves, it is a point of issue as to how much shortening of the P-R interval there must be in order to prove that the impulse arises in the A-V node rather than in the auricular tissues adjacent to it. Theoretically, there should be a shortening in the P-R interval of at least 0.03 second, the time consumed by the impulse in passing from the S-A to the A-V nodes.¹⁰ Confusing factors may, however, enter in. Thus, in the presence of vagal stimulation depressing A-V conduction, there may be, coincident with the descent of the pacemaker, a lengthening of the P-R time.¹¹

In the tracings in which the P wave does not appear and is buried in the Q R S (ventricular) complex, it is not always clear whether

7 Levine, S. A. The Action of Strophanthin on the Living Cat's Heart, *J. Exper. M.* **29** 493, 1919.

8 Barker, L. F., and Richardson, H. B. An Unusual Combination of Cardiac Arrhythmia of Atrial Origin Occurring in a Patient with Focal Infection and Thyroid Adenomata, *Arch. Int. Med.* **23** 158 (Feb.) 1919.

9 Carter, E. P., and Wedd, A. M. Observations on the Occurrence of inverted and Diphasic P Waves in Lead III of the Human Electrocardiogram, *Arch. Int. Med.* **23** 16 (Jan.) 1919.

10 Lewis, T. The Mechanism and Graphic Representation of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 189.

11 White, P. D. Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, *Arch. Int. Med.* **25** 423 (March) 1920.

the unseen P is upright or inverted. Again, an apparently absent P wave may mean that it has become so greatly flattened in that particular lead as to be isoelectric, though it might appear as a distinct wave in another lead. Another possibility when the auricular complex is absent is standstill of the auricle, described by White¹²

A further consideration is the lead in which the abnormality appears, for inversion of P in Lead III is not so significant as inversion in Lead II. In tracings made on 700 cases, mostly cardiacs, Goddard¹³ found inversion of P in Lead III seventy-five times and in Leads I and II only eleven times. Barker and Richardson,⁸ on the other hand, among 400 records found but one showing inverted P waves. In the eleven cases of variation of P waves in this study, all but two showed the abnormality in Lead II.

Because the disturbances in this series were transient and the patients were being operated upon, there was no opportunity for experimentation on the effects of atropin, vagal pressure, etc. We did not have, as did Wilson in his report of A-V rhythm occurring after the injection of atropin, the benefit of simultaneous venous tracings. It would appear certain, however, that all these cases represent various stages of the same process, viz., a dislocation of the pacemaker. (In the cases of auricular-ventricular dissociation¹⁴ one might more properly speak of a doubling of the pacemakers.) In most of the cases, possibly in all, the pacemaker, or where there are two, one of the pacemakers arises in the A-V node. Because we cannot be certain that all of these are cases of A-V rhythm, we shall designate them simply as the group showing a marked dislocation of the pacemaker.

HEART RATES IN RELATION TO DISLOCATION OF THE PACEMAKER

Dislocation of the pacemaker is explained on the theory either that the rate of the S-A node falls below that of the A-V node, in which case the latter becomes the pacemaker, or that the A-V node is stimulated to a rate above that of the S-A node. In either instance the rates during normal and abnormal rhythm might differ. The heart rates for cases showing dislocation of the pacemaker were charted and found to fall into three classes. Four cases showed a slower rate during the abnormal rhythm. The heart rate of one of

12 White, P. D. Auricular Standstill, an Unusual Effect of Digitalis on the Heart with Special Reference to the Electrocardiograph, Boston M. & S. J. **175** 233, 1916.

13 Goddard, C. H. Changes in the P Wave of the Human Electrocardiogram, Arch. Int. Med. **16** 133 (July) 1915.

14 White, P. D. Ventricular Escape with Observations on Cases Showing Ventricular Rate Greater than that of the Auricles Arch. Int. Med. **18** 244 (Aug.) 1916.

these is illustrated in Figure 12 A. Here after the beginning of operation, whenever the heart rate fell to 125 or below there was an absence of P waves in the electrocardiographic record. In one instance, the heart rate was faster during the period of abnormal rhythm (Fig 12 B). In six of the cases, the rate bore no relation to rhythm. This group is illustrated (Fig 13) by the case which showed on R-P interval. As seen in the chart, the rhythm changed on three occasions without a change in rate.

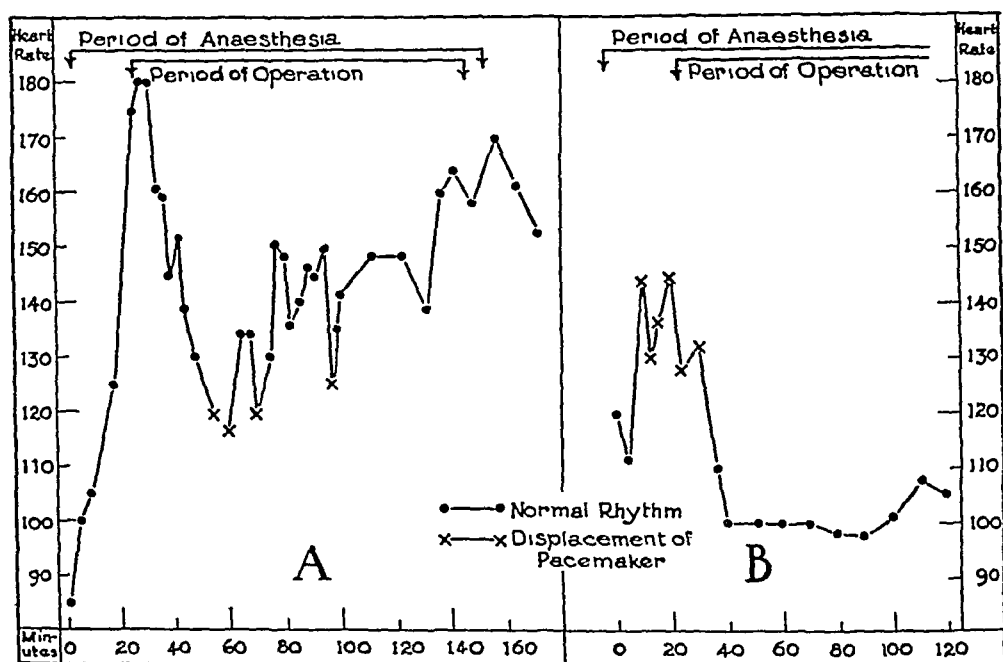


Fig 12—A Note the slower rate which occurs with the displacement of the pacemaker. B Note the faster heart rate which occurs with the displacement of the pacemaker.

FACTORS IN PRODUCTION OF ABNORMALITIES

In discussing the cause of the abnormalities noted, it is necessary to consider various factors. Twenty-four (48 per cent) of the cases show some disturbance of the heart beat not present in the preliminary tracings. Eleven of these are classified as showing displacement of the pacemaker (some show other changes as well), thirteen as showing other abnormalities. The number of cases is too small and the factors concerned are too numerous to permit definite conclusions. The following analyses must therefore be regarded simply as interesting observations.

Sex.—Twenty-three of the persons operated on were males, and twenty-five were females. Sex bore no relation to the incidence of abnormality.

Age—The age of patients varied from 2 to 84 years. Twenty-six were under 40 while twenty-two were over 40 years. The incidence of abnormality for those under 40 was nearly the same as for those over that age.

Cardiovascular Symptoms—A history of serious infection (scarlet fever, rheumatic fever, chorea, tonsillitis, pneumonia, etc.) was not more common in those yielding abnormal tracings than in the normal group. A history of cardiac symptoms (dyspnea, edema, etc.) was, on the other hand, of some importance. Only 11 per cent of those with normal tracings gave a story of cardiac disturbances, whereas 41 per cent of those with abnormal tracings reported such difficulties.

Cardiac Lesions—Only four of the forty-eight persons showed definite signs of cardiac disease by routine physical examination. Two

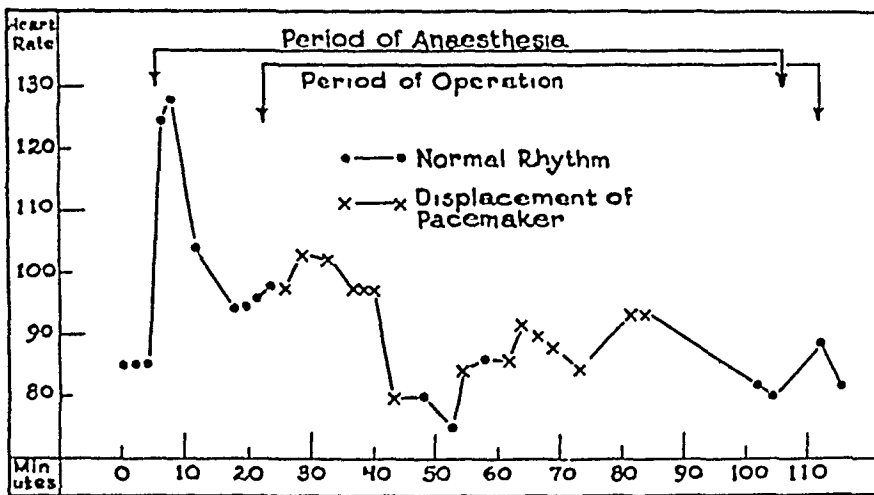


Fig 13—Note that a change of rhythm occurs in three instances without a change of rate

of these (one a case of mitral stenosis and the other of chronic myocarditis) showed abnormal preliminary tracings and the other two (one a case of mitral regurgitation and the other of sclerotic aortic valves) showed some abnormality during operation. In only one case did the condition of the heart cause serious debate as to the advisability of operation. This was a woman with a permanent auricular fibrillation and mitral stenosis who had had repeated attacks of gallstone colic. She was thoroughly digitalized so that on the morning of operation there was no pulse deficit. In order to determine whether a pulse deficit occurred during operation, the anesthetist signaled the times at which she counted the pulse, and simultaneously electrocardiographic records were made. During the period of induction of anesthesia the auricular impulses broke through the digitalis block and the heart rate jumped to 150, while the pulse rate did not exceed 100. In this instance there

was without doubt a real pulse deficit. During the period of actual operation, however, there was no deficit. Cholecystectomy was performed without any difficulty and the patient left the hospital in satisfactory condition.

Blood Pressure—With due consideration to the age of the patients, five of forty-five patients had high blood pressures, and nine had pressures which seemed to be low. Abnormality of blood pressure in this series bore no relation to abnormality of the heart mechanism.

Position During Operation—Normal records were obtained more frequently in those patients who were placed flat on the table than in those in other positions. It is probable, however, that other factors were operative in these cases.

Preliminary Medication—Thirty-seven of the patients received preliminary morphin (usually 0.01 gm.) and atropin (0.0005 gm.). Seven received morphin only and six had no preliminary medication. Wilson¹⁴ has shown that for from eight to fifteen minutes following the injection of 1 mg. atropin, vagal stimulation produced an A-V rhythm in the majority of his twenty cases. The abnormal rhythm could not be produced after twenty minutes had elapsed. In this series the atropin would not be expected to cause A-V rhythm, for the dose was only one half that used by Wilson and at least thirty minutes intervened before the beginning of the observations. Of the thirty-seven cases receiving atropin, six (16 per cent.) showed a disturbance of the pacemaker, of the thirteen cases not receiving atropin, five (38 per cent.) showed this change. The preliminary atropin would seem to diminish rather than increase the chances of inducing the abnormal rhythm. Concerning morphin, Cohn¹⁵ has shown in dogs that the action of the drug is similar to vagus stimulation. In our forty-four cases receiving morphin, however, eight patients had disturbances of the pacemaker, while of the six not receiving it, three showed these changes. The observations are too few to warrant any conclusions as to the role that morphin may play in the production of abnormalities.

Lack of Oxygen—The work of Greene and Gilbert¹⁶ suggests that anoxemia may be a factor in producing A-V rhythm, for, of their twenty-one soldiers who breathed air having a low oxygen tension, six showed this disturbance. In none of our cases was there any apparent lack of oxygen, although the routine anesthetization in the operating room did not provide any accurate data on this point.

Type of Anesthesia—All of the anesthetics were given by one of a staff of three trained anesthetists. Twenty of the patients received

¹⁵ Cohn, A. E. The Effect of Morphin on the Mechanism of the Dog's Heart After Removal of One Vague Nerve, *J. Exper. M.* **18** 715, 1913.

¹⁶ Greene, C. W., and Gilbert, N. C. Studies on the Responses of the Circulation to Low Oxygen Tensions, *Arch. Int. Med.* **27** 517 (April) 1921.

ether, thirteen by the open drop method and seven through an intra-pharyngeal tube, using the Connell apparatus. Twenty-two had nitrous oxid and oxygen, and eight had local anesthesia (procain). The abnormal rhythm occurred in seven (35 per cent) of the cases receiving ether, in three (14 per cent) of those receiving gas-oxygen and in one (12 per cent) of those who had procain. It was present in but 15 per cent of the cases in which ether was given by the drop method but occurred in 70 per cent (five out of seven) of the cases in which ether was given by means of a nasal tube introduced into the pharynx. Considering all forms of disturbances of the heart mechanism, abnormalities were not more common with one kind of anesthesia than with another.

Length of Anesthesia and Operation—The longest period of anesthesia was three hours and five minutes and the shortest twenty-two minutes, the average being eighty-five minutes. Abnormalities were more frequent in the longer procedures than in the shorter ones.

Type of Operation—The distribution of operative fields was as follows: head, six; throat and neck, seven; chest, one; intra-abdominal, nineteen; extraperitoneal, eleven; extremities, six. The chief differences were noted between operations involving the head and neck and those on other parts of the body. Of the former, 70 per cent showed some type of abnormality in the electrocardiograph record, while of the latter 40 per cent were abnormal. The fact that head operations were longer than those of other types does not account for this greater incidence of abnormalities, because abnormalities occurred in almost every case during the early part of the operation. A disturbance of the pacemaker was present in 46 per cent of the thirteen operations involving the region above the clavicles, and in only 13 per cent of all other operations. In several instances abnormality seemed to follow critical steps in the operative procedure, but in the great majority of cases no such relationship was evident.

Frequency of Records—In five of the eleven cases of disturbance of the pacemaker, the abnormality appeared in one or two records only. It is possible, therefore, that other cases presented abnormalities of which records were not obtained. For all those cases showing abnormality, the interval of time between records is the same as for those showing no abnormality.

Time of Occurrence—Figure 4 presents the time relations for cases showing premature beats (upper part) and disturbances of the pacemaker (lower part). In every instance except one the abnormal rhythm appeared during either the induction of anesthesia or the first third of the operation. This points to factors other than fatigue as a cause of this abnormality.

In reviewing the evidence in this study it seems that the incidence of a displacement of the pacemaker is greater in patients having head and neck operation, intrapharyngeal anesthesia, or when preliminary atropin is omitted. It is possible that vagal stimulation is in some way concerned in these procedures. The production of premature beats does not seem to be clearly related to any of the factors considered. None of the cases showing abnormal electrocardiograms gave clinical evidence during operation of an embarrassed circulation. Though abnormality in the mechanism of the heart beat occurred with surprising frequency these periods were transient and of physiological rather than clinical significance ¹⁷

SUMMARY

An electrocardiographic study of fifty cases was made during anesthesia and surgical operation.

1 In many cases the electrocardiographic tracings revealed a heart rate considerably faster than the pulse rate recorded by the anesthetist.

2 About one half of the cases showed some abnormality of the mechanism of the heart beat, not present in preliminary tracings, the most prominent being paroxysmal auricular tachycardia, premature beats, and marked displacement of the cardiac pacemaker.

3 Various factors which might contribute to the production of the abnormalities named are analyzed. Only those which might possibly be concerned with alterations in vagal tone, seem to be of importance.

4 The observed abnormalities of the heart beat were transient and unassociated with clinical signs of embarrassed circulation. In the main, they were of physiological rather than of clinical significance.

We wish to thank Dr. Harvey Cushing and his associates, as well as the staff of the operating room, for their generous cooperation in this study.

17 A table giving detail of cases appears in authors' reprints.

STUDIES ON THE PHYSIOLOGY OF THE LIVER

II THE EFFECT OF THE REMOVAL OF THE LIVER ON THE BLOOD SUGAR LEVEL¹

FRANK C MANN, M.D., AND THOMAS BYRD MAGATH, M.D.
ROCHESTER, MINN

In previous articles,¹ a method was described for the total removal of the liver from the dog, and a brief summary was made of the data obtained from a series of studies on the completely hepatectomized animal. The present report deals more in detail with one phase of our experiments, namely, the effect of hepatectomy on the sugar concentration of the blood.

Method for Total Removal of the Liver of the Dog—Since the method of removal of the liver has been fully described,¹ only a brief description will be given. The liver is removed in two stages. All operations are performed under ether anesthesia with aseptic surgical technic.

The first operation consists of a reverse Eck fistula, that is, lateral anastomosis of the portal vein and the vena cava and ligation of the latter on the cephalic side of the stoma. At first a considerable portion of the blood from the posterior portion of the body passes through the liver, but since the capillaries of the liver offer more resistance to the flow of blood than is necessary for the development of collateral circulation through the azygos and internal mammary veins, most of the blood soon passes by way of the latter channels.

The second operation consists in the ligation of the portal vein at its entrance into the liver. This causes all the blood from the viscera and hind legs to return by way of the collateral vessels, the azygos, and the internal mammary veins. If, as sometimes occurs, collateral vessels fail to develop sufficiently, as is recognized by congestion of the intestines after ligation of the portal vein, the occlusion of the portal vein is carried out in two stages. In such case the ligature is removed from the vein which is partially occluded by passing

* From the Division of Experimental Surgery and Pathology, The Mayo Foundation and the Section on Clinical Laboratories, Mayo Clinic.

1 Mann, F. C. Studies in the Physiology of the Liver. I. Technic and General Effects of Removal, *Am J M Sc* **161** 37, 1921. Also *Am J Physiol* **55** 285, 1921.

Mann, F. C., and Magath, T. B. II. The Liver as a Regulator of the Glucose Concentration of the Blood, *Am J Physiol* **55** 285, 1921. III. The Nitrogen Constituents of the Blood Following Removal of the Liver, *Am J Physiol* **55** 286, 1921.

Mann, F. C., and Magath, T. B. The Effect of Total Removal of the Liver, *Tr Sect Path & Physiol A M A*, 1921, p. 29.

a blood vessel suture through the center and ligating one side. At a later operation the portal circulation is entirely occluded. The third operation consists of removing the entire liver. This is accomplished without disturbing the general circulation.

Symptoms Following Total Removal of the Liver of the Dog—The clinical course of events is very definite and varies but slightly in different animals. Recovery from anesthesia and from the immediate effects of the operation is rapid. One hour after operation, the animal usually appears almost normal,² and remains so from three to eight hours. During this period the animal is to all appearances normal, it walks around, responds to call, exhibits the usual interest in other dogs, and drinks water.

The onset of the moribund period is usually sudden and the subsequent development of various symptoms typical and rapid. The first symptom noted is muscular weakness. The animal cannot hold itself erect, or avoid swaying when walking, and prefers to lie down. The muscular weakness develops quickly and in a short time the animal is unable to move any of its muscles, except those necessary for respiration. Coincident with this development of muscular weakness is a decrease and subsequent loss of reflexes. Usually, within an hour after evidence of muscular weakness is first noted, the animal lies quietly breathing, with muscles flaccid and relaxed. This period of flaccidity may be short, but in a few animals it has lasted for several hours. After a variable period, usually not more than one hour, there is a rather sudden return and exaggeration of the reflexes. Muscular twitchings develop, at first involving separate muscles or small groups of muscles, then general convulsions occur in one of which the animal dies. In typical experiments the animal vomits a few seconds before death.

The symptoms and the order of their occurrence are muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitchings, and convulsions. The development of these symptoms is extraordinarily constant. The average animal, if untreated after hepatectomy, dies within two hours after the appearance of the first signs of muscular weakness.

The blood pressure seems to be practically normal while the animal is active. When the first symptom develops, the blood pressure decreases but does not necessarily fall to a low level. The pulse usually becomes practically twice as rapid as normal. Just before death the rate may become slower than normal. The heart continues to beat

² In order to express the difference between the hepatectomized animal when not showing symptoms and at the stage just preceding death, "normal" and "moribund" have been employed. "Normal" means that the animal appears to be normal, "moribund," that the animal appears to be dying.

for a long time after breathing has ceased. The respiration undergoes certain changes following operation, varying with the condition of the animal. Often the animal is in coma, and Cheyne-Stokes type of respiration is noted. The temperature usually continues normal until the animal becomes flaccid, although just previous to the development of muscular weakness, it may rise one degree higher than it was before operation. It may become subnormal before death. Some of the

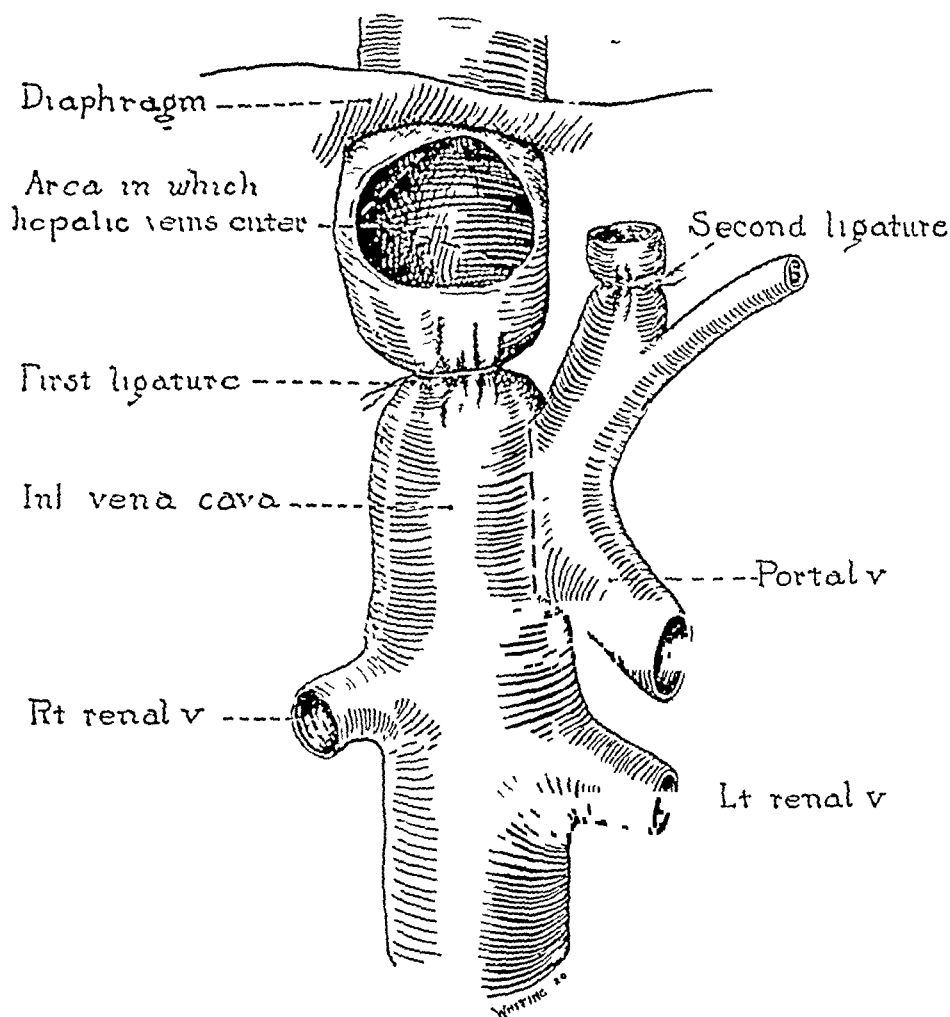


Fig 1—Diagram illustrating the steps in the technic of the removal of the liver. At the first operation the portal vein and vena cava are anastomosed along the dotted line and the first ligature is placed. At the second operation, after the collateral circulation has been established, the second ligature is placed. At the third operation the liver and the portion of the vena cava between the ligature and diaphragm are removed.

animals secrete practically a normal amount of urine before they develop symptoms, but others are anuric throughout the postoperative period.

Previous Observations on the Symptoms Occurring After Removal of the Liver—Some of the symptoms noted after exclusion or removal of the liver have been observed by previous investigators who particu-

larly noted the convulsions and coma Minowski³ observed these symptoms in some of his geese after extirpation of the liver Kausch⁴ particularly emphasized the occurrence of convulsions in his study of hepatectomized geese Hahn, Maassen, Nencki and Pawlow⁵ noted muscular twitchings, convulsions, and coma in dogs in which Eck fistulas had been made and the hepatic artery ligated Doyon, Gautier and Policard⁶ record the development of typical convulsions in frogs following removal of the liver Whipple and Hooper⁷ observed muscular twitchings in dogs with Eck fistulas and ligation of the hepatic artery Matthews and Miller⁸ report that animals in which the hepatic artery was ligated some weeks after the making of an Eck fistula became comatose from eight to twelve hours after the ligation

The study most comparable to ours was made by Perroncito,⁹ who removed the liver with little disturbance of the circulation, and the animals developed the characteristic symptoms of hepatic insufficiency His description of the symptoms corresponds quite closely to our own

The failure of previous investigators to observe the production of a definite group of symptoms may be owing to several causes In most investigations the experiments were performed in order to obtain definite data with regard to a particular fact concerning the liver, practically all the experiments were complicated by marked derangement of the circulation or by an anesthetic or narcotic so that symptoms could not be observed

In a large number of studies on hepatectomized animals the most pronounced and constant phenomenon which attracted our attention was a progressive, invariable decrease in the sugar content of the blood

Previous Work on the Effect on Blood Sugar of Removal of the Liver—The first experiments on the effect of exclusion of the liver

3 Minkowski O Beitrage zur Pathologie der Leber auf den Stoffwechsel III Ueber den Einfluss der Leberextirpation auf den Stoffwechsel, Arch f exper Path u Pharmacol **21** 41, 1886

4 Kausch W Der Zuckerverbrauch im Diabetes Mellitus des Vogels nach Pankreasextirpation Arch f exper Path u Pharmacol **39** 219, 1897

5 Hahn, M, Massen, O, Nencki, M, and Pawlow, J Die Eck'she Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen fur den Organismus Arch f exper Path u Pharmacol **32** 161, 1893

6 Doyon, M, Gautier, C, and Policard, A Lesions renales determinées chez la grenouille par l'ablation du foie Rappel aux textes Compt rend Soc de biol **64** 271, 1908

7 Whipple, G H, and Hooper, C W Icterus A Rapid Change of Hemoglobin to Bile Pigment in the Circulation Outside the Liver, J Exper M **17** 612, 1913

8 Matthews, S A and Miller E M A Study of the Effect of Changes in the Circulation of the Liver on Nitrogen Metabolism, J Biol Chem **15** 87, 1913

9 Perroncito A Sulla estirpazione del fegato, Riforma med **36** 830, 1920

on blood sugar seem to have been made by Bock and Hoffman¹⁰ They excluded the liver from rabbits by ligating the abdominal aorta, portal vein, and inferior vena cava between the entrance of the renal and the hepatic veins Specimens of blood were obtained from the heart by passing an obturator through the inferior vena cava Animals thus operated on lived from two to fifty minutes The blood sugar decreased, and no sugar could be found in the blood of animals living as long as forty-four minutes These experiments have been severely criticized by subsequent workers because the circulation is so greatly damaged by the procedure

Minowski,⁷ in his classical research on the effect of removal of the liver in geese, noted a decrease in blood sugar Seegen¹¹ excluded the liver in dogs by ligation of the aorta and vena cava above the

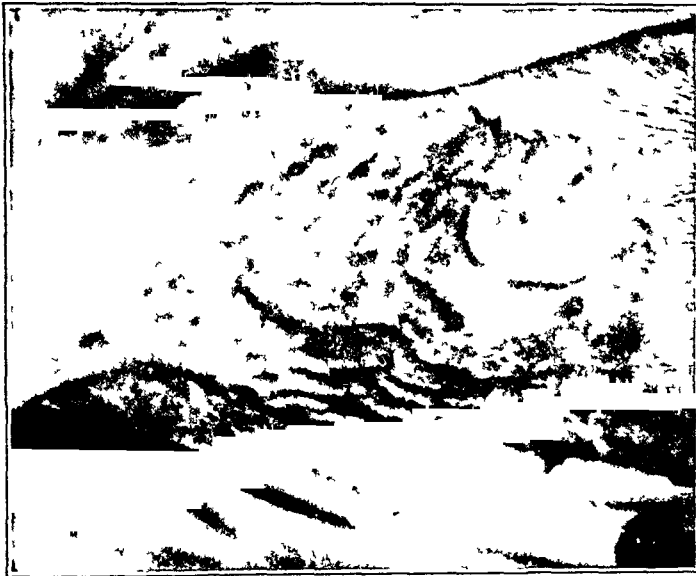


Fig 2—Side of the abdominal wall of animal showing the dilated veins of the skin which follow the operative procedures necessary to prepare the animal for total removal of the liver In many animals these veins do not dilate but the entire collateral circulation is developed through the great azygos vein

diaphragm The animals lived from twenty to seventy minutes A marked reduction in the blood sugar was observed Schenck¹² ligated the base of the liver, probably obstructing both the portal vein and the vena cava A decrease in blood sugar was noted Kaufmann¹³ repeated

10 Bock, C. and Hoffman, F A Experimental Studien uber Diabetes Berlin, H E Oliven, 1874

11 Seegen, J Die Zuckerbildung im Thierkarper, ihr Umfang und ihre Bedeutung, Berlin, A Hirschwald, 1890

12 Schenck, F Ueber den Zuckergehalt des Blutes nach Blutentziehung, Arch f d ges Physiol **57** 553, 1894

13 Kaufmann, M Nouvelles recherches sur la pathogenie du diabete pancreatique Compt rend Acad d Sc **118** 656, 1894, De l'influence exercée par la suppression partielle ou totale de la fonction hépatique sur la glycémie chez les animaux normaux et diabétiques, Arch de physiol norm et path **8** 151, 1896

The method of experimentation and length of life after operation, with the exception of experiments with geese, precluded any correlation between the reduction of blood sugar and the development of symptoms

Methods of Blood Sugar Estimation—A specimen of blood for estimation of blood sugar was obtained from the jugular vein before operation. The liver was removed under ether anesthesia and sterile technic. In most experiments another specimen of blood for the estimation of blood sugar was taken immediately after operation and then at hourly intervals until the animal was moribund. In a few experiments only two blood sugar estimations were made, one just before operation and the other when the animal became moribund.

The blood sugar concentration was estimated by the Benedict¹⁶ modification of the Lewis-Benedict method. Our collaborators, who made most of the estimations, had had an enormous experience with this method in the clinical laboratory, the records of which could be used as controls of our estimations. Moreover, it was early foreseen that it would be necessary to make a very large number of blood sugar estimations, and this method was preferred for quantity work. After the investigation was well under way, parallel estimations were run by two other methods, that of Folin and Wu¹⁷ and Maclean's¹⁸ modification of Bang's method, each of which was very difficult to employ in estimating low concentrations of blood sugar. Hitherto, most studies in blood sugar have dealt with normal or high values, our investigation dealt mainly with subnormal and very low values. For these reasons the Benedict modification of the Lewis-Benedict method was most satisfactory.

It is recognized that there may be substances other than glucose in the blood capable of reducing picric acid or copper sulphate. It is possible that in our determinations the results have included some of these substances. However, this in no wise invalidates our general results for in each instance the same condition resulted in the same rises and falls and, as will be shown, the evidence is overwhelming in substantiating the statement that glucose only was being determined.

All the work has been controlled carefully. The operative work and the taking of blood specimens was done in one laboratory by one group of workers and blood sugar estimations were made in another laboratory by another group of workers. The specimens of blood were immediately marked with the animal's number and the specimen number.

16 Benedict, S. R. A Modification of the Lewis-Benedict Method for the Determination of Sugar in the Blood, *J. Biol. Chem.* **34** 203, 1918.

17 Folin, O., and Wu, H. A System of Blood Analysis. Supplement I. A Simplified and Improved Method for Determination of Sugar, *J. Biol. Chem.* **41** 367, 1920.

18 Maclean, H., and de Wesselow, O. L. V. The Estimation of Sugar Tolerance, *Quart. J. M.* **14** 103, 1921.

and sent to the laboratory. The worker who made the blood sugar estimations had no knowledge of the character of the experiment. At the conclusion of the experiment the data from the two laboratories were correlated, thus completing the experiment.

In a few experiments estimations of the glycogen content of the muscles were made before and after removal of the liver, the method employed for the separation and estimation of the glycogen was that described by Pfluger¹⁹

The Effect of Environmental Factors on the Blood Sugar—The effect of the operative procedure for obtaining the specimen for blood sugar estimation has been repeatedly emphasized as a complicating factor in all experimental data on blood sugar²⁰. It is undoubtedly

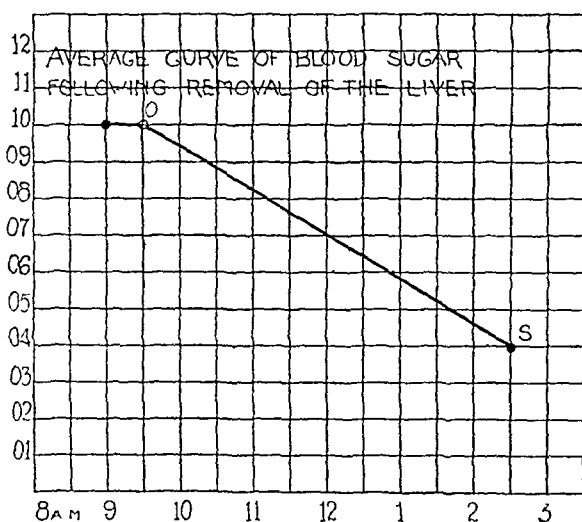


Fig 4—The average change in blood sugar noted in thirteen dogs following removal of the liver. O Point at which the liver was removed. S Point at which the animal became moribund.

true that such a procedure, or any procedure which may excite or frighten an animal, may cause a change in blood sugar. In our experience of several thousand blood sugar estimations on dogs, such a

19 Pfluger, E. Meine Methode der quantitativen Analyse des Glykogens und die Eigenthümlichkeit der Substanzen des Thierleibes, Arch f d ges Physiol **129** 362, 1909.

20 Pavy, F. W. An Enquiry Into the Effects on the Blood and Urine of the Intravenous and Subcutaneous Injection of Various Carbohydrates Standing in Relation to Animal Life, J Physiol **24** 479, 1899.

Scott, E. L. The Content of Sugar in Blood Under Common Laboratory Conditions, Am J Physiol **34** 271, 1914.

Shaffer, P. A. On the Normal Level of Blood Sugar of the Dog, J Biol Chem **19** 297, 1914.

Boehm, R. and Hoffmann, F. A. Beiträge zur Kenntniss des Kohlenhydratstoffwechsels. Arch f exper Path u Pharmacol **8** 271, 1878.

Cannon, W. B. The Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, Am J Physiol **33** 356, 1914.

complicating factor is of very slight significance in most experiments. Our observations show that if blood sugar estimations made every quarter or half hour, for a period of four to six hours, are plotted against the time, the resulting graph is practically a straight line. The effect of environmental factors could only be of importance in experiments in which very slight changes of a hyperglycemic character were being observed. In the series of experiments reported in this paper, this factor was negligible because we were studying hypoglycemia.

The Results on the Blood Sugar Level of Total Hepatectomy in the Dog—In our experiments a decrease in blood sugar has always occurred after the total removal of the liver. Of greater interest, however, is the fact that the amount of blood sugar exactly paralleled

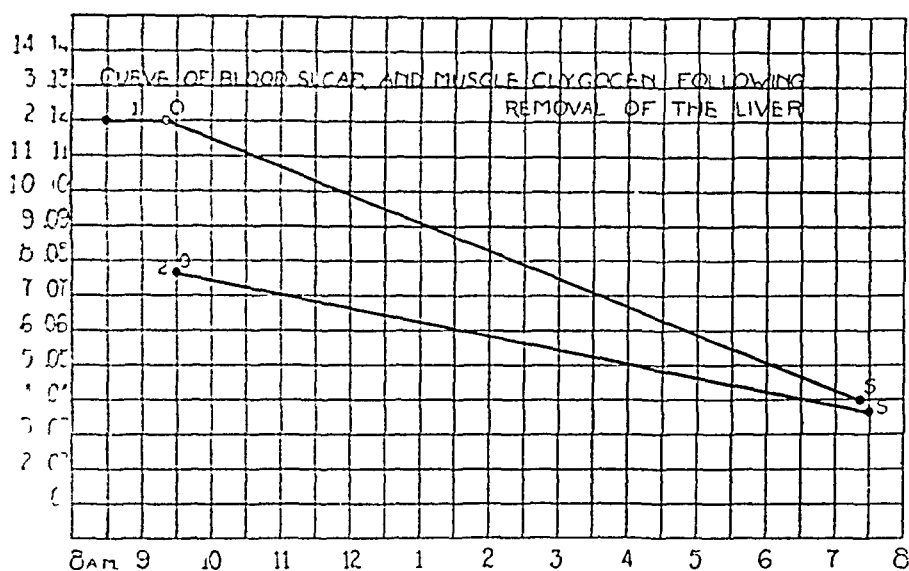


Fig 5—O Liver removed S Symptoms developed First curve shows decrease in blood sugar following removal of the liver Second curve shows parallel decrease in the muscle glycogen following removal of the liver

the clinical condition. The blood sugar in our animals before removal of the liver was usually slightly lower than the average for normal dogs. This is to be attributed to the fact that the portal blood supply of the liver had been deflected, as the average blood sugar of dogs with true Eck fistulas has also been slightly below the average for normal dogs. The anesthesia and operative procedure of hepatectomy did not cause the hyperglycemia which is usually noted after anesthesia and operative procedure on normal dogs. The blood sugar concentration immediately after hepatectomy was the same or less than that preceding operation, and very rarely 0.01 per cent higher, it decreased during the period the animal appeared normal. The level of blood sugar at which the first symptoms developed was usually quite definite and coordinate in the different animals. In most of the dogs this was 0.05 per cent

In some instances the first symptoms were noted when the blood sugar was 0.06 per cent and often when it was 0.04 per cent. The blood sugar decreased quite rapidly after the onset of convulsions and at the time of death was usually not in excess of 0.03 per cent. This direct relationship of blood sugar and the development of symptoms and death was so constant that the blood sugar could be estimated correctly after an examination of the animal's clinical condition when it showed symptoms.

The Effect of Hepatectomy on the Glycogen Content of the Muscles
—In one carefully performed experiment a specimen of muscle was

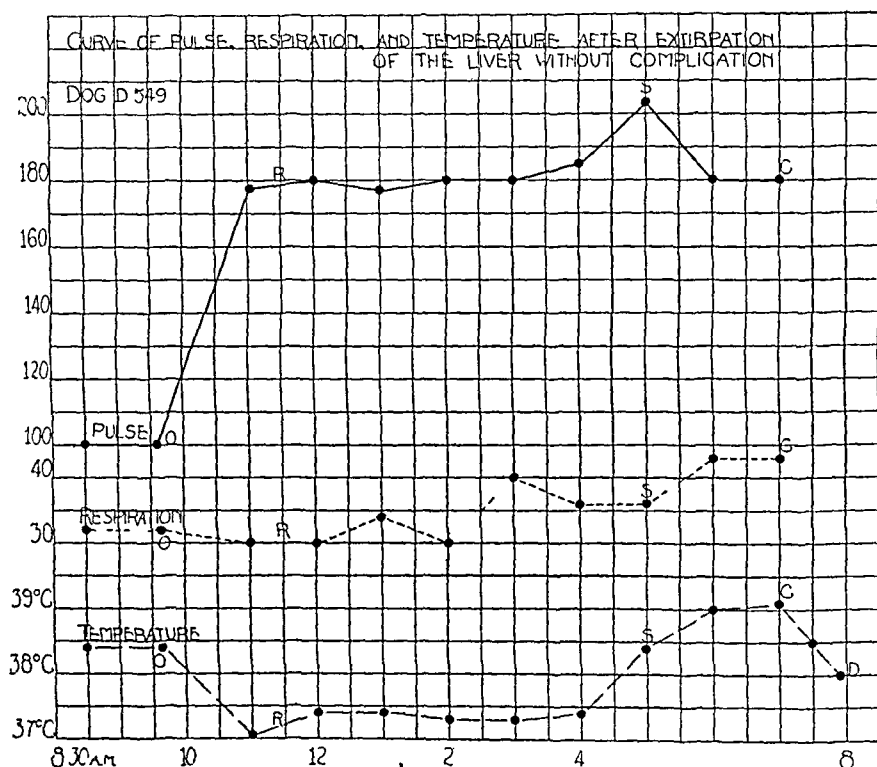


Fig 6—O Liver removed R Animal appeared normal S First evidence of muscular weakness C Convulsions D Animal died

excised at the same time the liver was removed. When the animal became moribund, another specimen of muscle was taken. An estimation of the glycogen content of these two specimens of muscle revealed that the glycogen had decreased about 50 per cent.

The Effect on Blood Sugar of Removal of the Liver of the Goose, Frog Fish, and Turtle—In all of these species the portal vein may drain into the general venous system without passing through the liver, and the liver is not so intimately related to the vena cava as it is in mammals. It is thus possible to remove the entire liver without obstructing the portal or vena cava circulation.

We have corroborated the findings of Minkowski and Kausch who obtained a reduction in blood sugar by removal of the liver from the goose. The effects of extirpation of the liver in the goose differ slightly from those obtained in the dog. The symptoms are not so marked and the blood sugar does not fall so low. The length of life after operation varied from eight to twenty hours. The main symptoms were muscular twitchings and convulsions.

The liver of the frog has been removed by other investigators. This species was of no value in our problem because the level of blood sugar in the normal animal is so low. In all the specimens of frog's blood examined the normal value was from 0.03 to 0.04 per cent. These observations were made on fasting frogs in captivity and the blood sugar might have been higher than this immediately after the animal was captured. The length of life after operation varied greatly in this species. Some frogs died within eight hours after hepatectomy, although one lived eight days. A frog might live normally for several days after total removal of the liver and then become flaccid and die within half an hour after the appearance of symptoms. They did not develop marked symptoms. At death the blood sugar was too low to estimate.

The fishes studied (gar pike and dogfish) had a high blood sugar, removal of the liver caused a marked decrease. The effect on the turtle, which normally also has a relatively high blood sugar value, was the same as on the fishes, namely a marked decrease of blood sugar.²¹

DISCUSSION

Our data prove conclusively that (1) the total removal of the liver is always followed immediately by progressive decrease in the sugar content of the blood, and (2) the development of the characteristic symptoms, which quickly led to death, exactly paralleled this decreasing blood sugar level. Certain symptoms appeared when a definite blood sugar value was reached, others occurred when the level had decreased, and death occurred at a fairly constant point in relation to blood sugar. These facts may be explained variously, but there are two main possibilities. The symptoms and death and the decreasing blood sugar may be dependent on some third unknown factor or factors, or, as is probably true, the blood sugar and symptoms may bear a relationship of cause and effect. Concerning the first possibility we have no data and at present it must remain as a mere possibility. It seems to us that the exact relationship between the blood sugar level and the development of symptoms and death following hepatectomy is based on cause and effect. The removal of the liver causes a decrease

21 These two species will be discussed in a separate paper

in blood sugar and when a certain point is reached, characteristic symptoms develop, when a lower level is reached death occurs

Why the blood sugar disappears after hepatectomy is another problem with two main possible explanations. Removal of the liver may allow some toxic substance in the blood to develop and combine, chemically or physically, with the glucose and this may be responsible for the symptoms and death of the animal. The truth of this is not supported by any evidence. A more plausible explanation of the cause of the decrease in blood sugar is that hepatectomy removes either the control of the sugar supply or sugar utilization, and the symptoms and death are actually due to a lack of glucose as food. Removal of the liver may produce a depletion in the carbohydrate material of the body either directly by removal of the store of carbohydrates and the place of its elaboration, or indirectly by removal of a substance which has to do with carbohydrate utilization. The latter possibility might be brought about in one of two ways (1) either directly by controlling the rate of glucose metabolism, or (2) indirectly by controlling the rate of protein or fat metabolism.

SUMMARY

There is a marked and progressive decrease in the blood sugar following total removal of the liver. The glycogen content of the muscles also decreases. Coincident with this decrease in blood sugar, a characteristic group of symptoms develop and progress until death occurs. This effect of hepatectomy on blood sugar has been observed in markedly different species, namely, dog, goose, turtle, and fish. In each species investigated, removal of the liver produced a marked decrease in blood sugar. The relationship of the decrease in blood sugar and the development of the characteristic symptoms seems to be one of cause and effect.

THE ELIMINATION OF ARSENIC IN THE URINE OF SYPHILITIC PATIENTS AFTER INTRAVENOUS INJECTION OF ARSPHENAMIN*

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Although the literature on arsphenamin has become extremely voluminous, yet there are relatively few reports of work done on the important subject of arsenic elimination after intravenous injection of this drug in which the arsenic determinations have been made by modern, accurate methods. Moreover, the older literature from 1910 to 1913 deals mostly with the intramuscular and subcutaneous methods of administration which are no longer in vogue today. For this reason, it has been deemed advisable to reinvestigate this subject on a series of carefully controlled patients with the use of more recent and acceptable methods.

REVIEW OF THE LITERATURE

The literature up to 1913 has been thoroughly reviewed by Ullman¹. We have gone over this literature and after thorough analysis, have decided to omit from this discussion the work of those authors² who used inadequate methods for the destruction of the organic matter of the urine or tissues or for the quantitative determination of arsenic.

Frenkel-Heiden and E. Navassart³ in 1913 published carefully obtained data on arsenic elimination after intravenous injections of arsphenamin. They used the sulphuric and nitric acid method for destroying organic matter and the Marsh mirror method for estimating arsenic as metallic arsenic. After a dose of 0.6 gm they detected in the urine during the first three days after injection 5.10, 1.40 and 0.08 mg, respectively, of arsenic. This gives 6.58 per cent elimination in three days. During the next ten days small amounts, 0.15, 0.80, 0.10, etc., to 0.07 mg were detected. In another patient with the same dose (0.6 gm) only 1.6 per cent was eliminated in the first

*From the Dermatological Research Institute, Philadelphia (Investigations aided by funds accruing from the preparation of arsphenamin.)

1 Ullmann, K. Elimination and Storage of Salvarsan After Injection Into the Human and Animal Body, *Arch f Dermat u Syph* **13** 114, 511, 1912.

2 Abelin, J. Beginning and Duration of Elimination of Salvarsan in the Urine After Injection, *Ehrlich's Abhandlungen uber Salvarsan* **2** 45, 1911.
Greven, K. The Beginning and Duration of Elimination of Arsenic in the Urine After Treatment with Salvarsan, *Ehrlich's Abhandlungen uber Salvarsan* **1** 56-58, 1911.

3 Frenkel-Heiden and Navassart, E. Ueber das Schicksal des Salvarsans im menschlichen Korper, *Ztschr f Exper Path u Therap* **13** 531, 1913.

three days and somewhat larger quantities were eliminated during the succeeding ten days. The figures beginning with the first day are 1.8, 0.8, 0.2, 0.6, 0.2, 0.4, 0.1 mg arsenic, etc.—down to unweighable traces from the seventeenth to the twentieth day. With smaller doses (0.4 gm) their figures were similar: 5.6, 0.5, 1.1, 0.4, 0.1 mg, etc.—to 0.07 mg in one case and 0.5, 0.3, 0.7, 0.5, etc., to 0.1 mg in another case. In the latter case the feces showed on the corresponding days 4.6, 10.3, 7.3, 2.1, 1.0, 0.8, 0.9 and 0.5 mg arsenic, respectively. The amount of arsenic eliminated in the feces was therefore almost eight times as great as that in the urine.

Ullman,¹ who made many valuable contributions to the toxicology of arsphenamin, published a limited number of daily analyses on the urine and feces of patients receiving intravenous injections of arsphenamin. He used the hydrochloric acid potassium chlorate method for destroying organic matter and determined arsenic by the Marsh mirror method after converting it into a sulphide. His own check analyses indicate that 26 per cent of the arsenic was lost in the process of destruction of organic matter. In the urine of the first of his series of patients who received 0.4 gm arsphenamin intravenously, he detected during the first three days 3.9, 3.1 and 1.4 mg arsenic, respectively. This is equivalent to a total of 7 per cent of the amount of arsenic administered. With doses of 0.3 gm arsphenamin he found in one patient 4.6, 2.2 and 1.6 mg arsenic, respectively, during the first three days, and in another patient 8.2, 2.7, 0.3, 0.8 and 0.1 mg, respectively, during the first five days. The percentages of elimination during the first three days were 9.3 and 12.2 per cent, respectively.

The work of Wilcox and Webster,⁴ although very important from a toxicologic standpoint, unfortunately does not include daily analyses of the urines. For this reason it is difficult to make comparisons. We may say, nevertheless, that, in general, the quantities detected by them are not much different from ours. In a study of the feces of one case they determined daily eliminations of 1.06, 1.90 and 1.29 mg arsenic, respectively, making a total of 4.25 mg arsenic during the first three days following intravenous injection of a 0.6 gm dose of arsphenamin.

Almost simultaneously, Lockemann⁵ published extensive analyses, using an improvement of the Marsh mirror method. After an intravenous injection of 0.38 gm arsphenamin (114 mg arsenic) the amounts eliminated during the first thirteen days were 1.86, 0.36, 0.27,

4 Wilcox, W. H. and Webster, J. *The Toxicology of Salvarsan*, Brit M J **1** 473, 1916. Webster, J. *The Analyst* **41** 231, 1916.

5 Lockemann, J. *Vergleichende Untersuchungen über die Arsenausscheidung durch den menschlichen Harn nach Injektion verschiedener Arsenikalien*, Biochem Ztschr **78** 1, 1916.

0.29, 0.18, 0.03, 0.11, 0.07, 0.03, 0.05, 0.09, 0.02 and 0.04 mg, arsenic, respectively. This represents a total elimination of 2.98 per cent arsenic or 2.1 per cent during the first three days. Eight other cases injected with either arsphenamin or neo-arsphenamin in which analyses were not made daily, showed somewhat larger percentages of elimination.

The most recent work is that of Bergman⁶. He used the acid permanganate method of Lehmann for the destruction of organic matter in the urine and an original distillation and iodimetric method for determining arsenic. His paper is rather unique in that he studied the elimination of arsenic after minute doses of neo-arsphenamin, from 24 to 96 mg., and representing from 4.82 to 19.30 mg. metallic arsenic. He injected the drug both in a menstruum of the patients' own serums and in physiological solution of sodium chlorid.

In a series of three patients, using the smallest of these doses in menstruum of the patient's serums, he obtained the following percentage of elimination during the first three days following injection 45.2,⁷ and 45.2 per cent respectively. With the largest of the doses the corresponding percentages were 18.7, 12.1, and 19.6. When the drug was dissolved in physiological solution of sodium chlorid and injected into three other patients in similar doses, the percentages of elimination were 70.0, 39.8 and 5.3 with the smallest, and 48.0, 44.0 and 5.2 with the largest of the doses, respectively. Bergmann's work is intended to show that there is more rapid elimination, and, therefore, less storage when the drug is dissolved in saline, rather than in the patients' own serum. He recommends the latter method on the ground that there are fewer clinical "reactions" observed. It would seem to us that Bergmann has not studied a sufficient number of patients to warrant his conclusions. Moreover, when working with such minute amounts of arsenic, the errors in estimation and hence in calculation of percentages become very large.

METHODS OF INVESTIGATION

The present study was conducted on three cases of tertiary syphilis with optic atrophy. The patients were kept in a ward on a hospital diet and their water intake was controlled. Chemical studies of the blood which were made simultaneously have been reported in a separate communication by Weiss and Corson⁸. The injections of 0.6

⁶ Bergmann, H. The Retention and Elimination of Arsenic After the Administration of Salvarsan in Serum and Aqueous Solutions, *Biochem Ztschr* 90 348, 1918.

⁷ Data are given only for two days in which percentage eliminated is 24.9 per cent.

⁸ Weiss, C., and Corson, A. Chemical Studies of the Blood and Urine of Syphilitic Patients Under Arsphenamin Treatment, *Arch Int Med*, 1921 (in press).

gm doses of alkalized arsphenamin were always given at about 11 a m before breakfast. The drug was dissolved in about 120 c c of distilled water. The urines were collected quantitatively for twenty-four hour periods, preserved with toluene and analyzed within two or three days.

Before selecting the methods of analysis, including the technic for destruction of organic matter in the urine and the quantitative determination of minute amounts of arsenic, a comparative study was made by Messrs Gavron, Blatt and one of the authors of this Institute of several existing methods, including those of Fresenius and von Babo and the Marsh-Berzelius as described by Hawk⁹ and of the Scott¹⁰ and Bang¹¹ methods. A modification of the Green¹² iodometric microtitration method was finally adopted. A description of this technic as well as analytical figures with the various methods tested will be found in a separate report by Raiziss, Gavron and Blatt¹³.

RESUME AND ANALYSIS OF RESULTS

The details of the analyses, the intervals of injection and various notes concerning the patients are given in Tables 1 and 2. The dose was always 0.6 gm of alkalized arsphenamin administered intravenously in 120 c c of distilled water, given fortnightly, weekly or semi-weekly, as described below.

CASE 1—T M, male, aged 38. Optic atrophy (Table 1). Chancre ten years ago. Under continuous arsphenamin treatment during the past two and one-half years.

This patient showed normal values for blood urea, sugar and nonprotein-nitrogen before this study was begun. The details of the subsequent changes in the blood will be found in a separate communication⁸. Very small amounts of arsenic were found in the urine before injection, this patient having been under continuous treatment for many years. The patient stated he always suffered mild reactions after injections. After this dose of 0.6 gm, there was nausea and occasional vomiting which lasted until the next morning. During the first, second and third days, the following amounts of arsenic were found in the daily twenty-four hour specimens of urine: 7.39, 3.12 and 1.47 mg metallic arsenic, respectively. This is equivalent to an elimination of 63 per cent in three days. During the succeeding ten days the amounts gradually diminished until they reached a level of about 0.11 mg on the thirteenth and fourteenth days after the injection. A mild retention of nitrogen was indicated in the blood findings.

⁹ Hawk, P. B. *Practical Physiological Chemistry*, P. Blakiston's Son & Co. Philadelphia, 1918, pp. 476-478.

¹⁰ Scott, W. W. *Standard Methods of Chemical Analysis*, D. Van Nostrand Co., New York, 1918, p. 30.

¹¹ Bang, I. *Quantitative Determination of Arsenic in Urine*. *Farmaceutisk Revy Schweiz Apoth Ztg* 55:393, 1917.

¹² Green, H. H. *The Microtitration of Arsenic*, Union of South Africa Dept. Agriculture, Fifth and Sixth Reports 1916-1918, of the Director of Veterinary Research, Pretoria 5:541-550, 1918.

¹³ Raiziss, G. W., Gavron, J. L., and Blatt, A. C. *The Estimation of Minute Quantities of Arsenic in the Urine* (to be published).

A second dose of 0.6 gm was given a fortnight after the first. The "reaction" this time was much more severe. There was vomiting, oliguria, bile-tinged urine, diarrhea and pain in the legs. The blood findings indicated a more definite nitrogen retention. During the first three days there were eliminated 9.79, 4.22 and 2.59 mg metallic arsenic, respectively. This represents 8.8 per cent elimination. The succeeding days showed gradually declining figures, reaching a level of from 0.53 to 0.58 mg arsenic from the twelfth to the fourteenth days.

A third injection of 0.6 gm arsphenamin was followed by a mild reaction—vomiting and headache—until the next morning. During the first three days the elimination was 7.46, 2.80 and 2.09 mg arsenic, respectively, giving 6.56 per cent. There was evidence of mild retention of nitrogen in the blood during the next few days.

CASE 2—M. J., male, aged 38. Optic atrophy (Table 1)

This patient showed values for total nonprotein nitrogen slightly above normal before this study was begun. He had been under continuous arsphenamin treatment for the past two years and showed small amounts of arsenic in the urine. After an injection of 0.6 gm arsphenamin, there was a mild reaction characterized by vomiting. There was evidence of mild nitrogen retention in the blood following the injection. During the first three days, the amounts of arsenic eliminated in the urine were 2.12, 4.33 and 2.07 mg, respectively. This is equivalent to 4.5 per cent. In the vomitus 0.85 mg arsenic were detected. During the succeeding days the amounts of arsenic gradually fell, 0.69 mg being found during the last days of the fortnight.

CASE 3—K. W., male, aged 39. Optic atrophy (Table 1)

This patient had been under treatment for many years and showed traces of arsenic in his urine. His blood showed values of nonprotein nitrogen only slightly above normal. The injection of the first dose of 0.6 gm arsphenamin was followed by slight chills, but no other untoward reaction. There was no evidence of increased nitrogen retention in the blood after this or any of the succeeding injections. During the first three days there were eliminated 3.10, 1.15 and 1.36 mg arsenic, respectively, or 2.97 per cent. The amounts gradually diminished to small traces by the end of the fortnight. A second injection of 0.6 gm was then given, and the following amounts were eliminated daily: 6.85, 2.61 and 1.49 gm arsenic, or 5.8 per cent in three days. A third dose was now administered with the following results: 5.13, 3.23 and 1.35 mg arsenic, or 5.19 per cent. During the following days the figures were 2.61, 1.36, 1.57, etc., reaching a level of 0.44 mg arsenic at the end of the fortnight.

DISCUSSION

A glance at Tables 1 and 2 reveals the fact that very small quantities of arsenic, detectable only by very delicate methods of analysis, are found daily in the urine of syphilitic patients after intravenous injections of arsphenamin. Thus, after a dose of 0.6 gm containing from 1.87 to 1.886 mg arsenic, from 3 to 8.8 per cent was eliminated in three days and from 4.9 to 13.5 per cent in the course of a fortnight. By far the greatest amount of arsenic eliminated by the route of the kidneys is, therefore, found in the urine of the first three days after injection. During the succeeding days the amounts gradually decline until by the fourteenth day they usually fall to a level of from 0.1 to 0.05 mg, which approaches the limit of accuracy of the method used.

Having seen that in human syphilitic patients only a relatively small portion of the arsenic injected intravenously as arsphenamin is elimi-

nated by the urine during the first week or two after administration, it would be of interest to know the degree of distribution and storage in the various tissues. No complete data are at hand giving the exact distribution of arsenic in all the organs of the human or animal body after a given dose of arsphenamin. We have been able, however, to obtain an approximate picture by making calculations, using some of the accurate figures on arsenic distribution available in the works of the Navassarts, Ullmann, Willcox and Webster, Lockemann, Bergmann and Green, and Vierordt's¹⁴ excellent "anatomical, physiological and physical data and tables" as well as Stitt's "physiological normals"¹⁵ which give the weights of the various organs of the human body. Our calculations show that the liver, the skeletal muscles and the skeleton, the kidneys, intestine and spleen are the most important depots for stored arsenic. In order of concentration, per 100 gm of tissue, the liver is first, next the kidney and spleen and then the intestines. No data are available for some of the important human organs of elimination, such as the skin and lungs, as well as for other tissues, such as the heart, pancreas, omentum, etc. We have had to approximate these on the basis of published animal data and we have used the smallest figures,—0.5 mg per 100 gm of tissue.

A few striking facts from the literature deserve special comment at this place, the Navassarts,³ as indicated above, have found the elimination in the feces to be from eight to ten times as great as that in the urine. The duration of elimination of measurable quantities of arsenic is about the same, from fourteen to twenty days. The arsenic in the feces may be due to resorption from the bile, as suggested by Obregia and Carniol¹⁶ who detected arsenic in the bile twenty-five minutes after an intravenous dose of neo-arsphenamin. They also demonstrated the elimination of arsenic in the saliva. Pomaret¹⁷ also found 10 mg arsenic in 5 c c of dog's bile collected one hour after intravenous injection of 0.3 gm neo-arsphenamin. The fact that we have found arsenic in the vomitus (Case 2), four hours after injection, suggests that elimination may take place by the route of the stomach, as in the case of morphin.

Willcox and Webster⁴ found $\frac{1}{2}$ and $\frac{1}{3}$ mg arsenic trioxid in 100 c c blood in two cases one hour after intravenous injection of 0.6 gm arsphenamin.

14 Vierordt, H. Anatomische und physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediziner, Ed. 3, 1906, Jena.

15 Stitt, E. R. Practical Bacteriology, Philadelphia, P. Blakiston's Son & Co., 1918, p. 540.

16 Obregia, A., and Carniol, A. Sur l'élimination du neosalvarsan par la bile, *Compt rend de la Soc de biol* 78: 468, 1915.

17 Pomaret, M. L'élimination des Arsenobenzols, *La med* 2: 123, 1920.

Myers¹⁸ and Barbat¹⁹ in a joint study conclude

The blood serum contains more than five times as much arsenic as the clot, it averages only 8 parts per million, or 0.8 mg per 100 gm of blood. This fact proves, that within half an hour after the administration of 0.4 gm arsphenamin 75 per cent is fixed in the body cells. Spinal fluid withdrawn immediately after injection showed 0.2 part arsenic per million of fluid in 42 per cent of cases, 27 per cent of the cases showed only traces of arsenic, and 31 per cent were arsenic free. The spinal fluid withdrawn twenty-four hours after injection was arsenic free in one case out of twenty-six, two specimens showed traces of arsenic, the remaining twenty-three contained an average of 0.25 parts per million.

Ullman¹ found only questionable traces of arsenic in the perspiration of a patient treated with arsphenamin.

Young²⁰ in an interesting experimental study found, that if the serum of goats (previously injected with arsphenamin) is dialyzed, some of the arsenic is removed, but the rest is bound to the serum and can not be dialyzed nor does it give the usual qualitative tests for arsenic. Inorganic arsenic compounds do not behave in this way. Young concludes that it is the arsenic which is thus bound in the blood and tissues which is slowly eliminated in the urine and feces.

The duration of elimination of stored arsenic is a controversial subject. Some authors have detected traces of arsenic several months after the injection of a single dose of arsphenamin. Data on the intravenous method are meagre. Bailey and MacKay²¹ in a study of syphilitics suffering from toxic jaundice as a result of treatment with novarsenobillon (French neo-arsphenamin) combined with mercury, were unable to detect any arsenic in the urines taken from twenty-four to 157 days after the last treatment. These authors used the Gutzeit test.

SUMMARY

The elimination of arsenic in the urine was studied in three cases of tertiary syphilis which were under arsphenamin treatment and under observation in a hospital ward. Very small quantities of arsenic, detectable only by very delicate methods of analysis, were found in the daily urine. Thus, after a dose of 0.6 gm containing from 187 to 188.6 mg arsenic, from 3 to 8.8 per cent was eliminated in three days and from 4.9 to 13.5 per cent in the course of a fortnight. By

18 Myers, C. N. Determination and Distribution of Arsenic in Certain Body Fluids After the Injection of Arsenobenzol, Salvarsan and Neo-Salvarsan, U. S. Public Health Rep., Reprint No. 520, 1919 (May 2) pp. 881-890.

19 Barbat, J. H. Permeability of the Meninges to Arsenic in Paresis and Tabes, J. A. M. A. **70** 147 (Jan. 19) 1918.

20 Young, W. J. Fixation of Salvarsan and Neo-Salvarsan by the Blood After Intravenous Injection, Biochem. Jour. **9** 479, 1915.

21 Bailey, C. V., and MacKay, A. Toxic Jaundice in Patients Under Antisyphilitic Treatment, Arch. Int. Med. **25** 628 (Nov.) 1920.

TABLE 1—DAILY ELIMINATION OF ARSENIC IN URINE OF SYPHILITIC PATIENTS INJECTED INTRAVENOUSLY WITH ARSPHENAMIN

Patient	T M *			M J †	K W ‡		
Drug injected	Arsphenamin			Arsphenamin	Arsphenamin		
Dose (each)	0.6 gm			0.6 gm	0.6 gm		
Arsenic in doses injected	188.6 mg			188.6 mg	188.6 mg	186.8 mg	
Days After Injection	Mg Arsenic in Urine			Mg Arsenic in Urine	Mg Arsenic in Urine		
	First Dose	Second Dose	Third Dose	First Dose	First Dose	Second Dose	Third Dose
1	7.39	9.79	7.46	2.12	3.10	6.85	5.13
2	3.12	4.22	2.80	4.33	1.15	2.61	3.23
3	1.47	2.59	2.09	2.07	1.36	1.49	1.35
4	1.37	1.39		2.21	0.86		2.61
5	0.97	1.39		1.71	0.87		1.36
6	0.92	1.12		0.73	0.50		1.57
7	0.59	1.12		0.83	0.36		0.81
8	0.69	1.12		0.83	0.25		0.80
9	0.68	0.53		0.83	0.26		0.81
10	0.11	0.54		0.84	0.25		0.80
11	0.11	0.53		0.69	0.26		0.44
12	0.11	0.54		0.69	0.05		0.44
13	0.11	0.29		0.69	0.05		0.44
14	0.11	0.29					0.44
Total in first 3 days after injection	11.98	16.60	12.35	8.52	5.61	10.95	9.71
Percentage eliminated first 3 days	6.3%	8.8%	6.5%	4.5%	2.9%	5.7%	5.2%
Total elimination, entire period	17.75	25.46	12.35	18.57	9.34	10.95	20.23
Percentage eliminated entire period	9.4%	13.5%	6.5%	9.8%	4.9%	5.7%	10.9%

* This patient eliminated 3.14 mg arsenic in urine during a three day period of observation just prior to first injection

† This patient eliminated 9.81 mg arsenic in urine during a six day period of observation just prior to injection and 0.85 mg arsenic in vomitus four hours after injection

‡ This patient eliminated 0.85 mg arsenic in urine during a ten day period of observation just prior to first injection

TABLE 2—SUMMARY OF DATA ON PATIENTS STUDIED

0.6 Gm Doses of Arsphenamin (D R I)* Alkaline Sol	Values for Total N P N † Observed Before Dose Was Injected	Clinical Reaction to Injection	Highest Values for Total N P N † Observed After Injection	Total Mg Arsenic Eliminated During First 3 Days After Injection	Percentage of Arsenic Eliminated in Urine During First 3 Days After Injection	Total Mg Arsenic Eliminated During Interval Between Injections	Number of Days in This Interval	Percentage of Arsenic in This Interval
Case 1 T M, male, age 38 Optic atrophy								
First dose	24 to 30	Mild	39	11.98	6.3	17.75	14	9.4
Second dose	23	Severe	44	16.60	8.8	25.46	14	13.5
Third dose	35	Mild	38	12.35	6.5	12.35	3	6.5
Case 2 M J, male, age 28 Optic atrophy								
First dose	31 to 33.5	Mild	39	8.52	4.5	18.57	13	9.8
Case 3 K W, male, age 39 Optic atrophy								
First dose	28 to 35	None	31	5.61	3.0	9.34	13	4.9
Second dose	26.5	Very mild	35	10.95	5.7	10.95	3	5.7
Third dose	24.5	Very mild	24.7	9.71	5.2	20.23	14	10.9

* 0.6 gm arsphenamin (D R I) represents from 187 to 188.6 mg arsenic

† Values for total nonprotein nitrogen (N P N) are given in mg per 100 c.c. blood

far the greatest amount of arsenic eliminated by the kidneys is, therefore, found in the urine of the first three days after injection. During the succeeding days the amounts gradually decline until by the fourteenth day they usually fall to a level of from 0.1 to 0.5 mg. which approaches the limit of accuracy of the method used.

The following observations deserve special comment:

1 Only a small part of the arsenic derived from arsphenamin is eliminated by patients through the urine, 13.5 per cent being the highest amount in fourteen days.

2 The largest amount of arsenic is eliminated in the first three days, after that uniformly small amounts are found in the urine.

3 The elimination of arsenic is larger after the second and third doses are administered than after the first.

4 Using constant doses of 0.6 gm. arsphenamin, there is considerable variation in the amounts of arsenic eliminated during a given interval of time by any one patient as well as by different patients presumably in the same stage of the disease and treated under the same conditions.

5 The elimination of only small quantities of arsenic in the urine may be explained by the fact that a considerable quantity is eliminated through the feces and some is temporarily retained by the liver, kidneys, spleen, intestines and other parts of the body.

A review of the literature on arsenic elimination and storage, and of the fate of the arsphenamin molecule in the animal body is given.

We are indebted to Miss Anna Corson, B.Sc. for valuable assistance in this investigation.

A COMPARISON OF CAPILLARY AND VENOUS BLOOD IN PERNICIOUS ANEMIA

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AND

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Patients afflicted with pernicious anemia present many symptoms which differ strikingly from those of secondary anemia. One is the discrepancy between the general appearance of a patient with pernicious anemia and his blood count. Patients with secondary anemia having a red blood cell count of 2,000,000 or less, are not only weak and ill enough to be in bed, but have a pallor so marked as to be noticeable even to the most casual observer. In contrast with this, patients who have pernicious anemia may be up and around and may have color in the face and lips which is so good that one is often surprised at the finding of an extremely low red blood cell count, from 1,000,000 to 1,500,000. In fact, often their color is so good that the anemia is overlooked by their physicians. The pallor may be partly obscured by the lemon yellow tinge of the skin.

We have often wondered why patients with pernicious anemia retain their color so well. It might be accounted for, in part, by the fact that there is atrophy of the skin and mucous membranes which renders them abnormally transparent and thus they transmit well the red color of the little blood they possess.

It has seemed to us that there must be another factor, however, to account for this interesting phenomenon, namely, that possibly the red blood cells in this disease might have a tendency to lodge in the capillaries of the skin and therefore give a false impression concerning the gravity of the anemia. It seemed possible that one might determine whether or not this were a fact by estimating simultaneously the number of corpuscles in the capillary and venous blood and comparing the findings with those of normal blood.

We found a marked difference between the capillary and venous counts in all cases of pernicious anemia examined, whereas, in normal individuals the capillary and venous counts were practically the same. All the patients had a frank pernicious anemia with atrophy of the skin and mucous membranes, characteristic tongue, achylia and characteristic blood findings, with red cell counts of 1,000,000 or a little above when first examined. The high counts recorded were all due to the fact that the patients had been transfused some weeks or months prior to the time that the counts were made.

The capillary red blood cell count of patients with pernicious anemia was 1,264,000, or 19.3 per cent higher on an average than the venous counts made at the same time. In every case there was a marked difference, the most marked being 3,070,000 red blood cells in the capillary blood and 1,920,000 in the venous blood—a difference

TABLE 1—VENOUS AND CAPILLARY* BLOOD COUNTS IN PERNICIOUS ANEMIA

Date	Capillary Count	Venous Count	Reduction, per Cent	Remarks
Case 1				
Aug 31, 1921	2,400,000	1,840,000	23.3	Transfused 10/5/21
Sept 13, 1921	2,220,000	1,760,000	20.7	
Dec 1, 1921	4,040,000	3,480,000	13.8	Transfused 10/10/21 and 10/28/21
Case 2				
Oct 25, 1921	5,440,000	4,800,000	11.8	Transfused 1/28/21
Case 3				
July 29, 1921	3,380,000	2,280,000	32.5	Transfused 6/5/21 and 6/18/21
Oct 7, 1921	5,200,000	3,880,000	25.3	
Case 4				
Aug 30, 1921	6,400,000	5,800,000	17.2	Transfused 3/21/21
Sept 20, 1921	5,640,000	4,400,000	22.3	
Oct 1, 1921	6,240,000	5,520,000	11.6	
Oct 25, 1921	5,620,000	5,510,000	16.7	
Case 5				
Nov 28, 1921	2,240,000	1,600,000	28.5	Transfused 11/29/21
Dec 4, 1921	3,440,000	2,680,000	22.0	
Case 6				
Nov 28, 1921	4,960,000	4,200,000	15.4	Transfused 1/21/21
Case 7				
Nov 28, 1921	3,070,000	1,920,000	37.4	Transfused 10/21/21
Case 8				
Dec 23, 1921	1,280,000	960,000	25.0	Transfused 12/31/21
Jan 1, 1922	3,800,000	2,600,000	31.6	
Venous and Capillary Blood Counts in Normal Individuals				
Case 1	5,520,000	5,540,000		
Case 2	4,900,000	5,120,000		
Case 3	5,260,000	5,400,000		
Case 4	5,160,000	5,000,000		
Case 5	6,080,000	6,120,000		
Venous and Capillary Blood Counts in Secondary Anemia				
Case 1				
Jan 19, 1922	2,960,000	2,680,000	9.4	Transfused 1/28/22
Jan 30, 1922	5,440,000	5,360,000	1.3	
Case 2				
March 4, 1922	2,400,000	2,480,000	None	
Case 3				
Jan 30, 1922	5,280,000	5,200,000	1.2	Transfused 9/7/21 prior to making of counts
Case 4				
Jan 30, 1922	4,400,000	4,720,000	None	Transfused 1/23/22 prior to making of counts

* In making the capillary blood count a small slit was made in the lobe of the ear and the blood drawn up in a red counting pipet in the usual manner. For the venous counts a small amount of blood was drawn from an arm vein into a syringe and a count quickly taken from this.

of 1,150,000, or 37.4 per cent, the least marked being 6,240,000 red cells in capillary blood and 5,520,000 red cells in venous blood, a difference of 770,000 red cells, or 11.6 per cent. This difference was striking regardless of whether the counts were made when the counts were low or whether they were made after treatment by transfusion when the counts were high. In contrast with this, the difference between

the capillary and venous counts in normal individuals was not great in any case and did not exceed 12 per cent in a single instance, nor did it exceed 94 per cent in four cases of secondary anemia, two of which had been transfused shortly before the counts were made

It was noted that the venous blood of patients with pernicious anemia contained an increased proportion of small cells while the capillary blood contained an increased number of macrocytes. This difference between the venous and capillary blood was so striking as to leave no doubt as to its real existence. It has seemed to us that the large red cells of the blood of patients with pernicious anemia lag in the capillary bed while the smaller cells filter through and in this way account for the marked difference between the capillary and venous counts.

This view would be in harmony with physical laws which govern deposits made by streams of water which carry a sediment heavier than water. As a stream broadens it slows, its carrying power is thereby reduced, and part of its sediment is deposited. The larger particles of a given specific gravity are deposited first or lag along the creek bed while the smaller particles of the same gravity are carried on. We have a somewhat similar condition existing in the human body though modified no doubt by biologic laws. As blood reaches the capillary bed the stream broadens and slows. Furthermore, the pulse is lost. There should exist, therefore, a tendency for the larger red cells (which are heavier than serum) to lag and for the smaller ones to be carried along readily.

One could believe also that the larger red cells might be retarded in the capillary bed by a process of filtration. This may be a factor also but against this view is the fact that in only one of four cases of leukemia which we have examined was there a great difference between the capillary and venous white cell counts (lower specific gravity than red cells) in spite of the fact that the myelocytes were larger than the leukocytes and lymphocytes.

In the belief that more light might be thrown on the subject, capillary blood cell counts were made on four patients with pernicious anemia, two of whom (Cases 9 and 10) had been transfused several months previously. Blood was withdrawn from the arm veins without the use of a constricting tourniquet to distend the veins. After this blood was taken, a tourniquet was placed around the arm for one minute, tight enough (about 180 mm of mercury) to prevent arterial blood from entering the arm and venous blood from escaping. During this minute the hand was contracted and relaxed a number of times with a view of dislodging, if possible, any red cells which might have accumulated in the capillaries of the arm. The muscular contractions forced the blood out into the veins so that they became quite tense. At the expiration of the minute, the tourniquet was

removed for about two seconds and then quickly replaced at 180 mm of mercury. This was done for the purpose of allowing the blood in the veins to be replaced by blood from the capillary bed. Venous blood was then withdrawn and counts were made.

The results obtained by this procedure were quite interesting. In each instance the venous count taken while the arm was at rest and before a tourniquet was applied was much lower than the capillary counts taken from the lobe of the ear. The venous counts taken after constriction of the arm with tourniquets and exercise were higher in

TABLE 2—CAPILLARY AND VENOUS COUNTS IN PERNICIOUS ANEMIA BEFORE AND AFTER CONSTRICTION OF THE ARM AND EXERCISE

Case	Capillary Counts	Venous Counts Before Constriction	Venous Counts After Constriction and Exercise
9	4,085,000	2,505,000	3,125,000
10	3,230,000	2,670,000	3,190,000
11	1,440,000	880,000	1,120,000
12	2,880,000	2,240,000	2,560,000

TABLE 3—CAPILLARY AND VENOUS BLOOD COUNTS IN NORMAL PERSONS BEFORE AND AFTER CONSTRICTION OF THE ARM AND EXERCISE

Case	Capillary Counts	Venous Counts Before Constriction	Venous Counts After Constriction and Exercise
13	5,170,000	5,210,000	5,490,000
14	4,800,000	5,160,000	5,280,000
15	4,960,000	5,040,000	5,080,000
16	5,040,000	5,080,000	5,120,000

every instance than the venous counts taken while the arm was at rest—in fact, the difference was so marked in each instance that we feel sure had the venous counts been taken from veins without the aid of a tourniquet they would have been relatively lower than the ones obtained.

As a control, similar counts were made on four normal persons. The venous counts taken before and after constriction and exercise were essentially the same as the capillary counts.

We wish to suggest that the relatively good color of the skin and lips in patients with pernicious anemia might be accounted for, in part, by the fact that the capillary blood is richer in red corpuscles than the venous blood and for this reason is misleading and does not give the physician a correct idea of the gravity of the situation.

CONCLUSIONS

1. Capillary red blood cell counts on patients with pernicious anemia were on an average 17.6 per cent higher than similar counts made

on venous bloods at the same time. The difference was as great as 37.4 per cent in one case, and in every case it was 11.6 per cent or more.

2 Venous counts made after constriction of the arm with a tourniquet, combined with exercise of the hand, were materially higher than counts made before constriction of the arm, and when the hand was at rest.

3 An increased number of macrocytes was observed in capillary blood as compared with venous blood.

4 The striking difference between the capillary and venous counts is caused, we believe, by a tendency for the larger red blood cells (macrocytes) to lag in the narrow capillary bed where the rate of flow of blood is slow and the pulse is lost.

5 It is believed that this accounts, in part, for the circumstance that a patient with pernicious anemia may have relatively good color of skin and lips even though he may be gravely anemic. This is misleading and frequently obscures the real gravity of the situation.

We wish to thank Drs. L. S. Milne, L. F. Barney, J. T. Ferguson and A. J. Simpson for their kindness in referring Cases 2, 7, 10 and 11 to us for study.

STUDIES ON THE NATURE OF NONSPECIFIC PROTEIN IN DISEASE PROCESSES

IV BLOOD FRAGILITY, RETICULATION AND BLOOD CHEMISTRY [†]

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The nature and mechanism of the reaction caused by the injection of foreign protein into the blood stream is still obscure. Some light has been thrown on this remarkable phenomenon by various workers who have studied the changes in blood cytology, certain phases of blood chemistry and immunology which occur during this reaction. The nature of this reaction is still a matter of controversy. There are some who consider the foreign protein reaction as an anaphylactic phenomenon. Others do not agree. There is still so much to be known about this subject that any further information is of interest and value. Cowie ¹ in a very comprehensive review of the nonspecific protein reaction has summed up all the present day knowledge on this subject. Herewith we present a more detailed report of some studies on the blood following the intravenous injection of a nonspecific protein. We have investigated blood fragility, reticulated red cells, blood urea, nonprotein nitrogen, blood sugar and alkali reserve in patients who were being treated by intravenous protein injections as a therapeutic measure for arthritis, chorea and various eye infections. The doses varied from 100 to 750 million killed typhoid bacilli. The patients all reacted characteristically with chill and rise in temperature. The ages of the patients varied from 8 to 50 years.

Fragility of the Red Blood Cells—The method of Greenthal and O'Donnell ² was used. Six patients were studied. In one case four fragility determinations were made at varying intervals after the injection. Our results show a slight increase in fragility following foreign protein injections. In Case 4 the control determination showed an increased fragility. This patient, a man with an infected corneal ulcer, had received four injections of protein during the previous ten days. It is possible that these injections may have made his red blood

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¹ Cowie, D. M. New York State J. M. **21** 395, 1921.

² Greenthal and O'Donnell. Am. J. Dis. Child. **22** 212, 1921.

cells more fragile Raphael and Sherman,³ using the same method, in a study of the fragility of the erythrocytes in psychopathic patients receiving foreign protein injections likewise found a slight increase in fragility after the injection At any rate the increase is not marked enough to be of significance (Table 1)

The percentage of reticulated red cells before and at intervals following the protein injection was determined in eight patients The patients were examined during various injections, one during the first injection, three during the second and third, and one during the sixth injection At no time during the protein paroxysm were we able to find any marked change in the number or character of these cells They were always within normal limits This was contrary to our expectations as examination of the blood smears after protein injection

TABLE 1 —EFFECT OF FOREIGN PROTEIN ON THE FRAGILITY OF THE RED BLOOD CELLS

Case	Control	After Injection		Remarks		
1	0 425-0 325*	0 450-0 325	Blood drawn 1 hour after injection, during chill, temperature 101 F			
2	0 425-0 325	0 425-0 325	Four hours after injection, temperature 102 6 F			
3	0 425-0 300	0 425 0 325	Six hours after injection, temperature 101 8 F			
4	0 450-0 350	0 450 0 375	Three hours after injection, fifth injection of foreign protein increased fragility due to repeated injections?			
5	0 425-0 325	0 450 0 350	Four hours after injection, temperature 104 F			
6	0 425 0 325	<u>½ Hour</u>	<u>1½ Hours</u>	<u>3 Hours</u>	<u>5 Hours</u>	
		0 450-0 325	0 450 0 325	0 475-0 350	0 425-0 325	

* 0 425-0 325 = Beginning hemolysis, 0 425 per cent saline, to complete hemolysis, 0 325 per cent saline

RETICULATED RED BLOOD CELLS

Method Capillary pipets were coated and dried with several layers of a vital blood stain (Unna's polychrome methylene blue, in citrated saline solution) The blood was quickly drawn into the capillary tubes and after from ten to twenty minutes a drop was blown on a slide and examined Six hundred cells were counted each time The efficacy of the stain was determined by examining the blood of normal adults and infants, patients with simple anemias, and one case of hemolytic family icterus

tions shows an increase in nucleated red cells, blood platelets and myelocytes If the reticulated red cell is an embryonal cell, one might think that there would be an increase during the protein reaction, for the bone marrow is stimulated to send forth new cells However, in none of the patients, both children and adults, were the reticulated cells increased with large doses of dead typhoid bacilli (Table 2)

3 Raphael and Sherman Am J Psychol 1 31, 1921

Urea Nitrogen—The results of the blood analysis show nothing remarkable during the protein paroxysm. The urea nitrogen was within normal limits at all times. It made no difference whether the determinations were made during the first or eighth injection of typhoid vaccine. There was a slight rise in the urea nitrogen usually between four and eight hours after the injection. This corresponded usually with the highest temperature. It does not seem as though the intravenous injection of typhoid protein causes any appreciable change in the urea nitrogen of the blood. Certainly it was not above normal limits in any reaction. Hisanabu⁴ found a marked increase in the urea nitrogen of the blood of guinea-pigs during peptone intoxication and

TABLE 2—EFFECT OF FOREIGN PROTEIN ON THE PERCENTAGE OF RETICULATED RED CELLS

Before Injection		Hours After Injection												Remarks
Case	Control	½	1	1½	2	2½	3	4	5	6	7	8	9	
1	0.7*	1.4		1.2	1.0		1.4	0.6		0.9	1.0			1st injection 300 million bacilli
2	0.6	0.6	0.5	0.3	0.8	0.6	0.7	0.6	0.4	0.6	0.5	0.7		2d injection 300 million bacilli
3	0.6		0.6		0.3			0.2	0.3	0.5	0.4	0.4		3d injection 500 million bacilli
4	1.2	1.1	0.8	0.6	0.7	0.6	1.0	0.8	1.1	0.8	0.6	0.8		2d injection 500 million bacilli
5	1.0	0.4	0.2	0.3	0.5	0.8		0.4	0.6		0.6			3d injection 750 million bacilli
6	1.6	1.2	1.0	1.5	1.1	1.2	1.6	1.4	1.8	1.1	1.4	1.6		2d injection 500 million bacilli
7	1.4	1.8	0.5	0.9	0.6	1.4	1.2	1.1	1.2					3d injection 750 million bacilli
8	0.6	0.5	0.2	0.6	0.5	0.4	0.3	0.5		0.6	0.5	0.4		6th injection 500 million bacilli

* Expressed in per cent

UREA NITROGEN AND TOTAL NONPROTEIN NITROGEN

Method The urea nitrogen of the blood was determined by the Van Slyke-Marshall method. The total nonprotein nitrogen was determined by the method of Folin and Wu. On some of the patients both the urea and total nonprotein nitrogen were determined at the same time. On others only one of the two determinations was performed. The patients on whom the determinations were made were fasting during the time of the experiment. A blood sample was drawn in the morning, after a twelve-hour fast, and then the typhoid vaccine injected. Blood was then drawn at varying intervals during the day. The experiments were made at various injections.

anaphylactic shock The negative results in these experiments suggest that so-called protein shock is an entirely different phenomenon from anaphylactic shock or peptone poisoning (Table 3).

Total Nonprotein Nitrogen—The results of these experiments agree closely with those on the urea nitrogen. There is very little evidence of protein destruction in the body during the protein paroxysms as

4 Hisanabu Am J Physiol 1 357, 1919

TABLE 3—EFFECT OF FOREIGN PROTEIN ON THE UREA NITROGEN OF THE BLOOD

Before Injection		Hours After Injection											Remarks	
Case	Control	½	1	1½	2	3	4	5	6	7	8	9		10
1	16.5*		16.2		15.0	18.6	12.0	15.6	18.0	14.2	18.0	15.6		1st injection 350 million typhoid bacilli
2	7.8			8.9		9.0		10.1		9.8		9.6		2d injection 500 million bacilli
3	15.0	17.8			19.2			12.0			15.1			4th injection 600 million bacilli
3	12.6			13.2			13.4					15.0		5th injection 600 million bacilli 5 days later
4	10.1		14.2		7.2	11.4	10.2	16.2	15.0	8.6	8.4	9.6		3d injection 500 million bacilli
5	7.5		7.5		7.6			13.4				9.6		1st injection 400 million bacilli
6	7.7				8.4		11.7		11.2		9.5		9.2	3d injection 750 million bacilli
7	15.1		14.2			16.2			16.2			16.8		1st injection 300 million bacilli
7	10.2		9.2		12.0		10.8				11.4			2d injection 500 million bacilli 4 days later
8	10.6		13.5		11.7		17.3	16.2	10.1	13.7		9.7	9.5	7th injection 600 mill on bacilli
9	13.4				10.1		7.8		10.6		16.8		12.3	1st injection 400 million bacilli

* Expressed in Mg per 100 C c

TABLE 4—EFFECT OF FOREIGN PROTEIN ON THE TOTAL NONPROTEIN NITROGEN OF THE BLOOD

Before Injection		Hours After Injection											Remarks
Case	Control	½	1	2	3	4	5	6	7	8	9	10	
1	34.6*		38.1	36.1	23.1	33.6	37.5	34.8	34.8	25.2	31.2		8th injection 600 million
2	25.4			22.8		24.3		24.1		27.3		26.7	3d injection 700 million
3	29.9		30.0	28.7	28.4	39.8		29.6	28.1		26.0		2d injection 500 million
4	32.9	23.1		25.7		21.1				29.5			4th injection 600 million
5	19.6	19.6	21.4	18.7		19.6		17.6				22.5	5th injection 600 million
6	27.5		36.6	37.5	36.6	38.1	33.9	35.7	37.5	39.0	33.1		1st injection 350 million
6	26.0		30.5		33.6		29.0		30.4		26.4		2d injection 500 million
6	32.9				32.1				35.2		31.6		3d injection 600 million
7	34.0			33.6		30.4		25.6		31.5		26.2	1st injection 400 million
8	26.1	25.7		26.1		23.4				23.4		24.4	1st injection 300 million

* Expressed in Mg per 100 C c

would be shown by an increase in the non-protein constituents of the blood. The very slight increase in non-protein nitrogen between the fourth and eighth hours can probably be accounted for by the fever which was highest at that time. Hisanabu found a marked increase in nonprotein nitrogen in the blood of guinea-pigs who were suffering from anaphylactic shock. Jobling⁵ found some increase in the non-protein nitrogen after the intravenous injection of dead typhoid bacilli. Working with rabbits Pepper and Miller⁶ found no change in the total nitrogen and urea of the urine after a single intravenous injection of dead typhoid bacilli. The results of the urea and non-protein nitrogen analyses of the blood of patients after the intravenous injection of dead typhoid bacilli form substantial evidence against the theory that protein and anaphylactic shock are similar (Table 4).

Carbon Dioxid Capacity of Blood Plasma—The method of Van Slyke was used. Three patients were studied after the foreign protein injections, two during the first injection and one during the fifth injection. The results of these experiments show that there is a slight diminution in the alkali reserve of the blood plasma during the protein paroxysm. This we think is not great enough to be of any practical importance. We have never seen any of our patients show any serious symptoms of acidosis. Eggstein⁷ studied the alkali reserve during protein and anaphylactic shock. He quotes the result of one experiment on man. A patient given twenty million dead typhoid bacilli into the vein showed a carbon dioxid capacity of 45.9 volumes per cent one hour after the injection. Her carbon dioxid capacity before the injection was 55.8 volumes per cent. In animals a much severer grade of acidosis was produced. This could be overcome by the injection of sodium bicarbonate. In anaphylactic shock in animals the acidosis was so marked as to endanger life. Death could not always be prevented by the use of sodium bicarbonate. Here, again, we find a difference between so called protein and anaphylactic shock (Table 5).

Blood Fat—Cowie and Hoag⁸ have shown in their studies on blood fat¹ that the total lipoids decrease during the protein paroxysm induced by the intravenous injection of dead typhoid bacilli apparently to a more marked degree than they do in fasting subjects who have not received an injection of foreign protein. We are indebted to them for the privilege of reporting their detailed results here (Table 6).

Blood Sugar—The method of Folin and Wu was used. Six patients were studied at various injections. The patients were fasting during the period of observation. The results of the blood sugar

5 Jobling J A M A **65** 515 (Aug 7) 1915

6 Pepper and Miller J Infect Dis **17** 694, 1916

7 Eggstein J Lab & Clin M **6** 481, 555, 1921

8 Cowie and Hoag J A M A **77** 1493 (Nov 5) 1921

experiments show nothing remarkable. There is a slight rise in the blood sugar during the height of the fever which quickly returns to normal. We have also run blood sugar analyses by the Benedict method on the same blood samples. They also give the same readings always, however, somewhat higher than with the Folin test. The rea-

TABLE 5—EFFECT OF FOREIGN PROTEIN ON THE CARBON DIOXID CAPACITY OF THE BLOOD PLASMA

Before Injection		Hours After Injection								Remarks
Case	Control	½	1	2	3	4	5	8	24	
1	55.7*	51.9	57.6	54.6	47.5	50.0	50.1	51.2	54.8	1st injection 300 million
2	52.0	54.8	53.8	51.2	50.0	46.5	51.8	51.6	53.8	1st injection 600 million
3	58.7	57.9	56.1	55.6	52.2	55.7		56.3	56.0	5th injection 600 million, very little reaction

* Expressed in volume per cent

TABLE 6—EFFECT OF FOREIGN PROTEIN ON BLOOD LIPIDS

Before Injection		Hours After Injection									Remarks
Case	Control	½	2	3	4	5	6	7	8	9	
1	0.793*	0.811	0.793	0.798	0.756	0.756	0.753	0.757	0.715	0.722	Fasting, 3d injection 500 million
2	0.716	0.639	0.644	0.540	0.577	0.655	0.670	0.690	0.684	0.716	Fasting, 1st injection 600 million

* Expressed in per cent

TABLE 7—EFFECT OF FOREIGN PROTEIN INJECTIONS ON THE BLOOD SUGAR

Before Injection		Hours After Injection											Remarks
Case	Control	½	1	2	3	4	5	6	7	8	9	10	
1	0 098*	0 111	0 116	0 102				0 120					1st injection 300 million
2	0 105			0 110		0 129		0 137		0 135			3d injection 600 million
3	0 081	0 085	0 081		0 090		0 120				0 080		5th injection 500 million
4	0 101		0 110		0 120		0 114		0 115				2d injection 500 million
5	0 108		0 106	0 082	0 088	0 123	0 140	0 122	0 129			0 117	3d injection 400 million
6	0 105			0 102		0 087		0 083		0 119		0 108	1st injection 350 million

* Expressed in per cent

son for the increased blood sugar during the fever is not clear. One might surmise that it is due either to increased metabolism or to stimulation of the glycogen reserve (Table 7).

Our investigation of the blood changes after an intravenous injection of foreign protein (typhoid vaccine) lead us to the following conclusions:

CONCLUSIONS

- 1 There is a slight increase in the fragility of the red blood cells during the protein paroxysm
- 2 There is no change in the percentage of reticulated erythrocytes
- 3 There is a moderate rise in the urea and total nonprotein nitrogen of the blood at the height of the fever resulting from the protein injection
- 4 There is a moderate fall in the alkali reserve of the blood after the foreign protein injection This is of short duration and a normal reading is soon obtained
- 5 There is a decrease in total blood lipoids during the protein shock This decrease is perhaps more marked than that which is found in fasting subjects not receiving the protein
- 6 There is a slight rise in the blood sugar curve (Folin and Benedict) at the height of the reaction following the protein injection
- 7 We believe that the so-called protein shock and anaphylactic shock are different phenomena

DIETETIC TREATMENT OF CHRONIC ARTHRITIS AND ITS RELATIONSHIP TO THE SUGAR TOLERANCE *

A ALMON FLETCHER M B

TORONTO

The importance of diet in the treatment of chronic arthritis is a question on which there is today considerable difference of opinion. In practice, its effect, as a rule, is confused by the establishment of several forms of treatment at one time, such as the removal of infectious foci, rest in bed, electrotherapy and hydrotherapy and other hygienic measures. It is, however, the experience of many observers that improvement is often brought about by changes in diet alone. But as to the character of this change, difference of opinion also exists. Increase in diet is recommended by some and decrease by others, or reduction of proteins in one case and reduction of carbohydrates in another. Sometimes improvement has been so marked as to lead older clinicians to believe that the disease had a metabolic basis, but clinical and laboratory investigation has not offered much evidence to support this hypothesis. In fact, interest has been more directed toward the part played by bacteria in the causation of this disease, and recent work has resulted in the general belief that chronic arthritis—with the exception of those cases due to trauma, strain, gout, some neuropathy, scurvy and hemophilia—is the result of a bacterial process. It is, therefore, natural that the origin of such infection should be looked for, infectious foci removed, vaccines administered, and, if necessary, some form of nonspecific protein therapy utilized. These measures are often attended by marked success, but sometimes results are disappointing, and if improvement occurs, it is often of a temporary nature.

In spite of this belief that the condition is a bacterial disease, there are still clinicians who insist on the importance of diet in its treatment. Pemberton,¹ especially, has for many years advised careful dietetic regulation—recommending a general reduction of the food intake, and laying special stress on the restriction of carbohydrates. In our own clinic, we have been impressed with the value of this recommendation in many cases. And, further, in those cases which receive benefit from such treatment, there has been as much clinical evidence of infection as in those which are refractory to such measures. One case, in which

* From the Department of Medicine University of Toronto, and from the Medical Division of the Toronto General Hospital.

1 Pemberton, R. Use of Diet in Treatment of Chronic Arthritis, *Am J M Sc* **161** 517 (April) 1921.

a hemolytic streptococcus was isolated from the blood during the height of the arthritis, showed prompt and quite marked improvement with a sudden reduction of diet. This reduction was made about six weeks after the onset of the attack, while the patient was still in a febrile state, and the favorable course of the infection was undoubtedly brought about by the change in diet. It would seem, then, that in such cases, there is a relationship between the maintenance of an infection and an unsuitability of the diet to the patient. This unsuitability might be due either to actual lack of balance in selection of food or to some error in the metabolism of the patient.

In a metabolic study of chronic arthritis, Pemberton and Foster² observed that the rise in blood sugar, following the administration of 100 gm glucose, was both increased and prolonged. They further concluded that this lowering of sugar tolerance was roughly an indication of the severity of the disease—tending to return to normal as convalescence set in. If this were the case, a determination of sugar tolerance would not give any specific information bearing on a case, other than its severity, but our own figures were not in accord with this conclusion, for it was sometimes found that some of the mildest cases showed a well-marked decrease in the sugar tolerance, which might even persist after recovery, while cases of the severest type sometimes gave figures which varied but slightly from normal. This question then presented itself: Does the lowering of sugar tolerance call for reduction of diet, and is the degree to which this tolerance is lowered any indication of the probability of giving relief by such measures? With this question in mind, we present the records of 100 cases of chronic arthritis in which the sugar tolerance was determined and in which the effect of reduction of diet alone was studied.

Method of Treatment—The 100 cases represent a selection from 160 cases of nonpurulent arthritis admitted to the medical wards of the Toronto General Hospital, and a few cases seen outside. The remaining sixty cases could not be included for various reasons. Many patients recovered without special treatment, a few recovered after removal of some focus of infection, others left the hospital before treatment was adequately observed. The cases associated with gonococcal infections are not included. Following McCrae's³ classification, the majority of cases were of the periarticular type, with or without deformity, a few showed hypertrophic bone changes, and one or two cases showed both types of the disease. The duration of the condition is shown in the tables, and in no case was dietetic treatment started before six weeks after the onset. The patients who were

2 Pemberton, R, and Foster, G. L. Arch Int Med **25** 243 (March) 1920

3 McCrae. Oxford Med **4** 374, 1921

admitted to hospital were allowed to remain in bed for two weeks at least, and until the process appeared to have reached a more or less stationary stage. This was done because rest alone may result in considerable improvement or even recovery. A few patients were treated outside of hospital, and in these no changes were made in the manner of living, other than the change in diet.

Dietetic treatment was carried out as far as possible in a routine manner, without regard for the patient's tolerance for carbohydrates or for his former diet. At first various changes in diet were tried. Reduction of the carbohydrates to one fifth or less of the usual intake sometimes was followed by much improvement. But better results were obtained by a more general reduction, and the large majority of the 100 patients were treated in the following manner: three glasses of milk, 3 glasses of buttermilk, one-half grape fruit and one or two oranges a day for one week, then the gradual addition of such food as eggs, fish, fowl, meat, 5, 10 and 15 per cent vegetables, fruits, junkets and jellies, and finally, brown bread in small amounts. Patients who were underweight were allowed cod liver oil and cream. This increase was made so as to provide from 1,500 to 2,000 calories a day within four weeks' time. The improvement noted in the tables occurred within this period, and with one or two exceptions, if no progress had been observed, it was not found worth while to continue. But those who did well were recommended to adhere to the diet—many reported progress for several months, and a few found that a relapse set in if their former diet was indulged in too freely.

While the effect of this treatment was being observed, no other form of treatment was given. If foci of infection were removed, four weeks were allowed to pass, but often these foci were untouched until after the period of observation. No drug was given, and physiotherapy was not ordered. When necessary, the bowels were moved on alternate days by enemas, and in a few cases liquid petrolatum was given by mouth.

The Sugar Tolerance—The test was carried out as recommended by Hamman and Hirschman⁴. After a fast of fifteen hours, 100 gm glucose was given by mouth in 300 c c of water, with the addition of the juice of half a lemon, 250 c c of water was given at one and two hour intervals. Blood sugar determinations were made immediately before the administration of the sugar and one-half hour, one hour, two hours and three hours afterward. The half-hour determination did not appear to give any essential information in most cases, and was discontinued. In a few cases, it was convenient to obtain blood at one

⁴ Hamman, L., and Hirschman, F. I. Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, *Arch Int Med* 20: 761 (Nov) 1917.

and one-half hour intervals only—these two determinations being usually sufficient to establish the existence of definite lowering of the tolerance. All the determinations were done by the method of Folin and Wu,⁵ the blood, as a rule, being precipitated at the bedside and the colorimetric reading done the same day, the figures are given in mg per c c.

For the interpretation of the blood sugar readings, after the ingestion of 100 gm glucose, it appears that three aspects are to be considered: (1) the maximum figure obtained, (2) the time at which the maximum occurs, and (3) the time required for the return to normal. There is still some disparity as to what should be considered a normal reaction. In our own work, a figure above 1.7 or a failure to return to the original level in ninety minutes, has been taken as a disturbance in sugar tolerance. In health, the maximum is reached in less than sixty minutes. In many of the figures presented, the maximum occurred later than this, but as this point possibly was frequently missed, it cannot be considered specially. The striking characteristic of the figures presented is the height which many of the figures reached, and especially the delay in the return. This last point is well brought out by the method of determining the blood sugar at one hour or one hour and a half intervals. For purposes of comparison, an average was taken of the figures obtained after the administration of the glucose, either at the hour or at one hour and a half intervals. These averages take into account both the maximum reached and the delay in the return, and in the tables the cases are grouped according to these averages. Three arbitrary groups were selected: (1) those in which the average was less than 1.4, (2) those in which the average was from 1.4 to 2, and (3) those in which the average was greater than 2.

Table 1 shows that the figures obtained varied from those which fell within normal limits to those which might be considered as indicating frank diabetes. And, indeed, no line can be drawn so as to classify the cases into diabetics and nondiabetics. Of the 100 cases, twenty-four belonged to Group I, i. e., with the average of the figures obtained under 1.4, fifty-six belonged to Group II, with an average of from 1.4 to 2, and twenty belonged to Group III, with an average greater than 2.

As to the relationship of the sugar tolerance to the severity of the disease, none was found, as many mild cases were found to appear in the group with the low tolerance as in the group with the high tolerance, of the twenty most severe cases, six belonged to Group I, ten to

⁵ Folin, O., and Wu, H. System of Blood Analysis, a Simplified and Improved Method for Determination of Sugar, *J Biol Chem* **41** 367, 1920

TABLE 1—CASES IN WHICH THE BLOOD SUGAR AVERAGED LESS THAN 14 MG PER C C FOR THREE HOURS AFTER ADMINISTRATION OF 100 GM GLUCOSE

Case	Sex	Age	Duration Before Admission	Fasting Blood Sugar	½ Hour	1 Hour	1½ Hours	2 Hours	3 Hours	Average	Result of Treatment
1	M	23	9 mos	0.86		1.25		1.21	1.03	1.16	Improved
2	F	30	23 yrs	1.06		1.18		1.17	1.05	1.13	Improved
3	F	39	3 mos	0.82		0.93		1.30	1.10	1.11	No improvement
4	M	38	18 yrs	0.98		1.37		1.45	1.36	1.39	Improved
5	M	29	8 mos	1.05	1.67	1.73		1.07	1.16	1.32	No improvement
6	M	38	4 yrs	0.84	1.34	1.49		1.29	1.23	1.39	Improved
7	M	26	6 mos	0.99	1.47	1.53		1.44	0.71	1.24	No improvement
8	F	20	2 mos	1.11			1.57		0.94	1.25	Recovered
9	F	31	10 yrs	1.15		1.51		0.75	1.19	1.15	Improved
10	F	63	30 yrs	1.09		1.55		1.20	0.94	1.23	No improvement
11	M	32	2 wks	0.99		1.87		1.02	1.16	1.35	Improved
12	M	56	3 yrs	0.93		1.63		1.73	0.76	1.37	Improved
13	F	55	6 wks	1.28			1.17		1.19	1.18	Improved
14	F	61	5 yrs	1.05		1.70		1.11	0.90	1.23	Improved
15	F	56	1 yr	1.25		1.30		1.70	1.05	1.34	Much improved
16	M	27	6 yrs	1.26		1.75		0.95	0.79	1.16	No improvement
17	M	34	20 yrs	0.93		1.39		1.46	1.21	1.25	No improvement
18	M	33	2 yrs	1.10		1.33		0.97	0.74	1.01	No improvement
19	M	30	2 yrs	0.91		1.34		0.69	0.67	0.90	No improvement
20	M	26	4 yrs	0.95		1.33		0.77	0.77	0.95	No improvement
21	M	65	10 yrs	1.21			1.44		0.91	1.17	No improvement
22	M	40	6 mos	1.25		1.74		1.32	1.11	1.39	Improved
23	M	60	8 mos	1.00		1.27		1.06	1.24	1.19	No improvement
24	F	33	18 mos	1.12			1.00		0.80	0.9	Much improved

CASES IN WHICH THE AVERAGE WAS 14.2 MG PER C C

25	F	29	10 yrs	1.2		1.8		1.7	1.5	1.6	Much improved
26	F	38	4 yrs	1.3		1.7		1.8	1.3	1.6	Much improved
27	F	38	1½ yrs	1.1		1.3		1.8	1.75	1.61	Much improved
28	M	20	8 wks	1.1		1.5		1.9	1.3	1.42	Much improved
29	F	37	2 yrs	1.08	1.17	2.04		1.99	1.05	1.69	No improvement
30	F	35	3 mos	1.12	1.63	2.12		2.17	1.37	1.88	Much improved
31	M	40	3 yrs	0.97	1.56	1.82		2.54	1.55	1.97	Improved
32	F	32	1 yr	0.94	1.69	2.22		1.97	0.63	1.60	Much improved
33	M	54	7 wks	1.09	1.83	2.31		1.85	1.75	1.97	Much improved
34	F	34	3 yrs	1.05			2.10		1.60	1.85	Improved
35	F	39	2 mos	1.07			1.45		1.46	1.45	Much improved
36	M	17	2 mos	1.12	1.47	1.87		1.71	1.44	1.67	Much improved
37	F	28	6 wks	1.04			1.73		1.4	1.53	Recovered
38	F	48	20 yrs	0.87		1.52		1.67	1.19	1.46	Improved
39	T	60	1 yr	0.93		1.86		1.26	1.25	1.45	Much improved
40	T	35	2 yrs	1.24		1.98		1.61	1.18	1.59	Improved
41	F	24	1 yr	1.08		1.58		1.53	1.51	1.54	No improvement
42	F	40	2 wks	0.88		1.62		1.91	1.64	1.72	Much improved
43	F	60	15 yrs	1.10			1.75		1.44	1.59	Improved
44	T	28	4 yrs	1.65		1.94		1.54	0.97	1.48	Much improved
45	F	58	8 yrs	1.03		1.67		1.67	1.65	1.66	Improved
46	M	23	7 yrs	1.10		1.75		1.50	1.50	1.59	Much improved
47	T	35	11 yrs	1.17		1.98		1.42	1.22	1.54	Improved
48	M	35	1 yr	1.3		2.0		1.5	1.4	1.6	Much improved
49	T	52	18 mos	1.03		2.50		1.90	0.90	1.7	Much improved
50	F	45	2 wks	0.95		2.54		2.13	1.22	1.65	Recovered
51	M	45	10 yrs	1.17		2.16		1.87	0.94	1.65	No improvement
52	M	50	2 yrs	1.3		1.5		2.2	1.3	1.6	Improved
53	F	29	6 wks	1.2		2.15		1.6	0.95	1.56	Improved
54	M	49	2 yrs	1.1		2.2		1.55	1.1	1.61	Improved
55	F	36	8 wks	1.3		2.0		1.5	1.4	1.63	Much improved
56	M	47	9 mos	1.08		2.20		1.68	1.85	1.91	Much improved
57	F	54	1 yr	1.13			2.27		1.33	1.80	Much improved
58	M	57	8 yrs	1.12			2.07		1.74	1.90	No improvement
59	F	34	5 wks	1.20		1.53		2.00	1.41	1.71	Recovered
60	M	42	1 yr	1.13		2.00		1.47	0.95	1.47	Much improved
61	M	30	5 yrs	1.29		2.08		2.08	1.34	1.83	Much improved
62	M	47	7 wks	1.08		2.20		1.63	1.85	1.91	Much improved
63	F	35	1 yr	2.18		2.20		1.98	1.38	1.85	Improved
64	F	20	1 yr	1.18		2.41		1.92	1.29	1.87	Improved
65	T	26	8 mos	1.07		2.42		1.98	1.36	1.92	Improved
66	F	22	6 wks	1.00		2.00		3.10	1.40	1.83	Recovered
67	F	43	6 mos	1.2		2.2		1.85	0.75	1.60	No improvement

TABLE 1 (CONTINUED) —CASES IN WHICH THE AVERAGE WAS 14.2 MG PER CC

Case	Sex	Age	Duration Before Admission	Fasting Blood Sugar	½ Hour	1 Hour	1½ Hours	2 Hours	3 Hours	Average	Result of Treatment
68	F	45	2½ mos	0.95			2.68		1.11	1.89	No improvement
69	M	35	2 yrs	0.91		2.59		2.11	1.28	1.99	No improvement
70	M	31	6 mos	1.02		2.35		2.0	1.3	1.88	No improvement
71	M	36	6 mos	1.3		2.7		1.7	0.7	1.7	Much improved
72	M	52	6 mos	1.5		2.5		1.3	1.3	1.7	Much improved
73	F	37	8 yrs	1.25			1.56		1.67	1.62	Much improved
74	F	65	1 yr	1.28		2.44		1.79	1.16	1.79	Much improved
75	F	66	Many years	1.02		2.06		1.27	1.28	1.53	Much improved
76	M	34	1 yr	0.98		2.02		2.17	1.32	1.83	Improved
77	F	69	10 yrs	1.09		1.96		1.56	1.20	1.57	Improved
78	F	53	2 yrs	1.45			1.91		1.64	1.77	Improved
79	M	36	6 yrs	1.2		2.1		2.25	0.9	1.75	Much improved
80	F	49	10 yrs	1.2		2.0		1.9	0.9	1.6	Improved

CASES IN WHICH THE AVERAGE WAS OVER 2 MG PER CC

81	F	26	7 mos	1.29	1.78	2.77		2.17	1.79	2.22	Recovered
82	F	63	16 mos	1.02	1.90	2.42		2.27	1.58	2.09	Much improved
83	F	64	2½ yrs	1.09		2.17		2.53	2.15	2.28	Much improved
84	F	22	6 wks	1.00		2.60		2.90	2.10	2.53	Much improved
85	F	35	4 yrs	1.2		2.4		2.5	1.5	2.1	No improvement
86	F	14	2 mos	1.1		2.2		2.3	1.5	2.0	Recovered
87	F	55	4 yrs	1.27			3.03		3.06	3.04	Improved
88	F	54	6 mos	2.28		3.71	2.86	4.26	3.92	3.96	Much improved
89	F	52	8 mos	1.78		3.17		2.59	1.97	2.57	Recovered
90	F	64	6 mos	1.5		3.6		3.2	2.0	2.9	Much improved
91	F			1.71		3.51		3.64	2.51	3.22	Much improved
92	F	52	4 yrs	1.7			4.2		4.1	4.1	Much improved
93	F	61	10 yrs	1.3		3.14		2.68	0.86	2.22	Much improved
94	M	45	18 mos	2.2		4.5		4.6	3.8	4.3	Much improved
95	F	47	5 yrs	1.3		2.6		3.0	1.9	2.5	Much improved
96	F	32	5 yrs	1.0		3.47			2.75	3.11	Much improved
97	F	42	1 yr	1.4			2.1		1.9	2.0	Much improved
98	M	57	4 mos	1.1		4.2		1.4	0.67	2.06	Much improved
99	F	47	4 wks	1.1			2.55		2.0	2.27	Much improved
100	F	27	1 yr	1.34		3.70		3.30	3.10	3.37	No improvement

Group II and four to Group III. It may also be noted that there is no correlation between the figures obtained and the duration of the illness.

A division of the cases according to sex shows that in Group I fifteen are men and nine women, in Group II, twenty are men and thirty-six women, in Group III, two are men and eighteen women. The women, therefore, have a lower tolerance than the men.

An examination of the urine for sugar during the test was done in the earlier cases, but it was found that no glycosuria occurred, even when the blood sugar rose above 1.7 mg per cc for a short time, and also the urine would show the absence of sugar throughout the test in cases showing a rise to 1.7 and remaining near this point for three hours. The examination of the urine following administration of sugar could not be used as a substitute for the blood sugar readings, and as it did not provide any additional information bearing on the point in question, the examination was not continued.

The Result of Dietetic Treatment—The majority of the patients appeared to have received benefit by the treatment described. Of the

100 patients, eight recovered. These cases were necessarily of less severity than the average and had not gone on to permanent joint change. Forty-three were much improved, twenty-eight were improved and twenty-one showed no improvement. The improvement showed itself (1) in the objective signs, (2) in relief from the pain and distress suffered by the patient, and (3) in improvement in the general health. In the twenty-eight patients grouped as improved, the result was largely subjective without much objective evidence of change in the joint. The forty-six who were much improved showed change on examination of the joint, as evidenced by decreased swelling, decreased limitation of movement and relief of muscle spasm. In some of these cases the improvement was immediate and striking, and no doubt could be entertained that it was the direct result of dietetic treatment. In two cases, a fall in temperature of 2 degrees (to normal) occurred within forty-eight hours of instituting treatment. As a rule, however, improvement set in slowly, starting in three or four days and being well marked in two or three weeks. After a month of treatment further progress was slow, but it was often marked enough to justify continuance of the diet for many months in favorable cases. Improvement in general health was generally a feature of the progress. Many of the patients suffered especially from some form of chronic dyspepsia, such as eructations of gas, loss or marked increase of appetite and abdominal distress. These symptoms, with very few exceptions, were very much relieved by the dietetic régime, and sometimes entirely so. Constipation was present in the majority of the cases, often of a very obstinate form, and while at first this symptom might be aggravated somewhat, most patients at the end of their course of treatment would report at least considerable relief from this symptom. Three patients were relieved of chronic eczema. For the first week or two there was almost always some loss of weight. In a patient who was overweight this was desirable, and he was encouraged to reduce his weight further. Underweight was found to be no contraindication to the diet, for after a loss of from 5 to 10 pounds, no further loss was observed and sometimes the loss was followed by a gain to the original weight or even more. Patients who were underweight received as much benefit as did those who were overweight.

As to undesirable results of the treatment, one or two patients were unable to take milk and some other low diet was substituted. One patient had nausea and vomiting. This patient was found to have a heavy indicanuria and after a diet of vegetables, fruit and bread and butter for a week, he was able to continue with the program outlined. No other ill effects were observed as a result of the treatment.

These results are summarized in Table 2. A separate tabulation of the results with male and female cases shows that females are much more suitable for such treatment than males. The eight patients who recovered were women.

The Relationship of the Sugar Tolerance to the Effect of Reduction in Diet—In those cases described as improved, the measure of improvement is largely dependent on the statement of the patient and is more or less an uncertain quantity. These cases, therefore, have been considered together with those unimproved for the purpose of demonstrating this relationship. The recovered cases are considered with those much improved, as these cases showed definite objective changes as a result of the treatment. The results are shown in Table 3.

TABLE 2—SUMMARY OF THE RESULTS OF DIETETIC TREATMENT

	Total	Male	Female
Recovered	8	0	8
Much improved	43	14	29
Improved	28	10	18
Not improved	21	13	8
	100	37	63

TABLE 3—THE EFFECTS OF TREATMENT ON CASES GROUPED ACCORDING TO THE SUGAR TOLERANCE

	Average Blood Sugar Reading for Three Hours		
	Less than 1.4	1.4 to 2	More than 2
Recovery or showing objective improvement	3 (12.5%)	31 (55.3%)	17 (85%)
No objective improvement	21 (87.5%)	25 (44.7%)	3 (15%)

TABLE 4—ANALYSIS OF CASES ON BASIS OF SEX.

	Less than 1.4		1.4 to 2		More than 2	
	Men	Women	Men	Women	Men	Women
Recovery or showing objective improvement	0	3	12	19	2	15
No objective improvement	15	6	8	17	0	2

Table 4 shows a similar relationship of the results on the sugar tolerance when the male and female cases are separately analyzed.

These figures show that the response to reduction of diet in an arthritic is roughly proportionate to the reduction of the sugar tolerance. This relationship, however, is not without quite evident exceptions. Case 100, with an average over 3.3, was a well nourished woman without evidence of any focus of infection which might interfere with progress, yet no effect of any sort was observed as a result of the treatment, and after six weeks she gave it up. In Cases 85 and 87 some relief of symptoms was apparent without any objective change. Both patients, however, were sufficiently impressed with the value of

the treatment to continue with the diet for several months. One patient (Case 8), who had an almost normal tolerance, showed immediate improvement and has had no relapse after eighteen months. Cases 15 and 24 showed some improvement on examination, but this progress, however, was quite less than the average result. These cases, however, were decidedly the exceptions and it is felt that in a case with a low tolerance one is able to offer, with confidence, a good prospect of improvement, while, on the other hand, a case with normal tolerance seldom showed progress enough to encourage one to recommend this form of treatment as a routine procedure.

DISCUSSION

Many of the factors exerting an influence on sugar metabolism are still somewhat obscure, and the clinical significance of the glucose tolerance test is as yet uncertain. The test was originally introduced with the object of detecting the potential diabetic but the occurrence of a low tolerance in other conditions has rendered its use for this purpose somewhat unreliable when considered by itself. A low tolerance has also been accepted as evidence of some endocrine unbalance but its value here is as yet unproved. There is some evidence to suggest that a disturbance of the sugar tolerance is associated with infections, as suggested by Pemberton and Foster² and also by the studies of F. M. Allen⁶ and others on diabetics. Our own experience would bear this out. In one case a slightly lowered tolerance was converted into a very much lowered tolerance by the operation of tonsillectomy, and for three weeks the blood sugar remained above 3 for the three hours of the tolerance test. After four weeks the tolerance test returned to the original reaction. It is our opinion that this temporary disturbance of sugar tolerance was due to a lighting up of the infection at the site of the operation. As a general rule, the tolerance is increased by removal of foci of infection. It is reasonable then, to account for the lowering of tolerance in arthritis by the presence of an infection, and Pemberton suggests that the rationale of his dietetic treatment is that he is catering to a function weakened by infection. But, on the face of it, it is difficult to believe that in some of the milder causes of Group III such a disturbance in sugar metabolism could be brought about by the arthritic infection alone.

If the lowering of the tolerance is not the result of the disease process, it is quite possible that it is associated with the pathogenesis of arthritis. Clinical observation would seem to offer some support of this hypothesis. In one case we were able to produce an acute exacerbation of the disease by allowing carbohydrates freely, this was

⁶ Allen, F. M. Unpublished Studies on Diabetes quoted by Sherrill, J. W., J. A. M. A. 77:23 (Dec 3) 1921.

done three times in the same case Pemberton brought about a similar relapse in one of his cases in the same way When the former diet of the patients is scrutinized, it is often found to have been unbalanced, especially in excess of carbohydrate food, and the frequency of this observation is such as to suggest that it should be considered as a possible cause of the condition And, lastly, the results of treatment in the present series of cases would appear to have an important bearing on this point No explanation is sufficient which suggests that the treatment is directed simply toward the relief of some secondary process, for sometimes the response is so marked and so striking that one is convinced that the diet must be closely related to the origin of the disease, and the relationship of the sugar tolerance to these results would indicate that this origin is intimately connected in some way with the metabolism of carbohydrates

Further discussion of this subject may be speculative, but, perhaps, one or two more points may be brought up When various low diets were being tried, it was found that reduction of carbohydrates alone did not yield the best results, and the diet finally chosen was one which was not only low in calories but which was rich in vitamin content Results with this diet appeared to be favorable enough to suggest the existence of an actual vitamin deficiency Others, notably Thompson,⁷ have emphasized the importance of these accessory food factors in the diet of arthritics The addition, however, to the patient's former diet of food rich in vitamin was by no means as effective as the combination of vitamins with a subcaloric diet, as described, and if a vitamin deficiency exists in those cases which received benefit by reduction of carbohydrates, it is likely that carbohydrates play some part in the production of this deficiency McCarrison⁸ and Mellanby⁹ have found that carbohydrate excess is an important factor in deficiency disease, and Funk¹⁰ associates vitamin B with carbohydrate metabolism—reporting a hyperglycemia in beriberi Findlay, Paton and Sharpe¹¹ found a decreased sugar tolerance in a case of rickets McCarrison further believes that excess of fats as well as carbohydrates must be considered in the production of deficiency disease This fits in well with our own observations on the dietetic treatment of the arthritics who were overweight For in these cases, reduction of fat has always appeared beneficial, and, while reduction of fat has not been urged in

7 Thompson, F G Dietetics in Chronic Arthritis, Practitioner **103** 110 (Aug) 1919

8 McCarrison, R Studies in Deficiency Disease, London, 1921

9 Mellanby, E Accessory Food Factors in Feeding of Infants, Lancet **1** 856 (April 17) 1920

10 Funk, C Action of Substances Influencing Carbohydrate Metabolism in Experimental Beri Beri, J Physiol **53** 247 (Dec) 1919

11 Findlay, L, Paton, D N, and Sharpe, J S Studies in Metabolism of Rickets, Quart J Med **14** 352 (July) 1921

those underweight, it has been given in the form of cod liver oil and cream in moderation. Such a deficiency would also account for the relationship of diet with what appears to be a infectious disease, for it has been repeatedly found, as pointed out by McCarrison⁸ and Hess¹² that infections readily light up in deficiently fed animals.

If, then, excess of the energy bearing constituents of the food may induce deficiency disease, especially in the presence of inadequate vitamins and protein, and if infections are liable to appear before actual deficiency syndromes develop, it is a fair hypothesis that in the presence of some focus of infection lack of balance in the diet is a cause of chronic arthritis in a large number of cases, and that the results reported in this paper are due to measures directed toward the correction of this defect.

These considerations are presented with the full appreciation of the fact that one phase only of the treatment has been dealt with. If diet is a factor in the etiology of this disease, there are likely many others, as, foci of infection, exposure, fatigue and other disease. Influenza was the exciting cause in many of the cases studied, and these cases were sometimes among those most favorably influenced by diet. It is interesting to note that a low sugar tolerance may follow this disease (Cowie and Beavan¹³).

No special observations are included as to the value of other therapy for the object of the investigation was to study the value of diet alone, but after this had been observed, it was found worth while to institute other forms of treatment, especially hydrotherapy and physiotherapy. Foci of infection, when of considerable size, appeared to interfere with the favorable effects of diet, and it is recommended that these should always be looked for and, if possible, removed before dietetic treatment is started. One patient, however, recovered in spite of the existence of several abscesses at the roots of the teeth, which the patient had refused to have extracted. But such infectious foci were found only in a minority of the cases, and when removed none of the effects reported here could be attributed to this procedure.

The more favorable results, along with the considerably lower tolerance in women, might call for some comment. This might be associated with some fundamental difference in their metabolism, to their manner of living, or, perhaps, to their dietetic habits. Certainly, lack of balance in diet is more frequently found among women than among men, especially carbohydrate excess, with an inadequacy of protein. In this connection, it might be mentioned that reduction of protein in chronic arthritis, as is so often practised, appears to be productive of much harm.

¹² Hess, A. F. Newer Aspects of Some Nutritional Disorders, *J. A. M. A.* **76** 693 (March 12) 1921.

¹³ Cowie, D. M. and Beavan, P. W. *Arch. Int. Med.* **24** 78 (July) 1919.

CONCLUSIONS

1 Of 100 cases of chronic arthritis, reduction of diet alone appeared to result in the recovery of eight patients and in quite evident improvement in forty-three

2 The sugar tolerance was decreased in the large majority of these cases, and this decrease showed no relationship to the severity of the disease

3 Patients who have a low tolerance are much more frequently benefited by reduction in diet than those cases with a normal tolerance

4 In certain cases of chronic arthritis, dietetic regulation appears to be the most effective form of treatment, and while the value of such treatment in an individual case cannot be determined with certainty, the lowering of the sugar tolerance is a useful clinical indication for this procedure

5 Female patients derive greater benefit from such treatment than men, and, as a rule, they show a lower tolerance

VARIATIONS IN ALIQUOT FRACTIONS OF GASTRIC CONTENTS *

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In a previous paper ¹ attention has been directed to the fact that single determinations of gastric acidity by the Rehfuß method are not sufficient on which to base conclusions, because they do not take into account individual variation. Another important question which arises in evaluating results obtained by this method is whether the aliquot fractions aspirated are truly representative of the total gastric contents at the time of withdrawal. Recently, Gorham ² has shown that "the gastric chyme is not, in the majority of instances, a homogeneous mixture after a test meal, and that the acidity of different portions may vary widely." He found on the withdrawal in rapid succession of many samples that there was a marked variation in acidity of these samples in subjects having clinical evidence of gastric disease. Such variations were not so apparent in subjects without clinical evidence of gastric disease, although Wheelon ³ has reported some interesting variations in normal subjects.

PART I

In view of the important bearing of this observation on the errors involved in the Rehfuß fractional method of gastric analysis,⁴ the following experiment was conducted. A group of subjects showing no clinical evidence of gastric disease were given the standard Ewald meal after removal of the fasting contents. No further samples were aspirated until three-quarters of an hour had elapsed, whereupon the entire gastric contents were removed as rapidly as possible by the successive withdrawal of 10 c.c. samples. This procedure usually required ten or fifteen minutes. The acidity of the samples was then determined in the usual manner by the titration and colorimetric methods ¹. The results are presented in Figures 1, 2, 3, 4, 5, 6 and 7. Figures 1 to 5 represent the graphs of psychotic subjects, while Figures 6 and 7 are of normal individuals.

* Read at Society for Experimental Biology and Medicine, Jan 18, 1922

* From the Department of Bacteriology, Psychiatric Institute of the New York State Hospitals, Ward's Island

1 Kopeloff, N. Individual Variation as Influencing the Rehfuß Fractional Method of Gastric Analysis, *J A M A* **78** 404 (Feb 11) 1922

2 Gorham, F. D. Variations of Acid Concentration in Different Portions of the Gastric Chyme, and Its Relation to Clinical Methods of Gastric Analysis, *Arch Int Med* **27** 434 (April) 1921

3 Wheelon, H. Relation of the Gastric Content to the Secretory and Motor Functions of the Stomach, *Arch Int Med* **28** 613 (Nov 15) 1921

4 Editorial Critique of Gastric Analysis, *J A M A* **77** 202 (July 16) 1921

TABLE 1—VARIATION IN 10 Cc FRACTIONS REMOVED IN RAPID SUCCESSION BY THE RUSSELL TUBE THRU QUARTERS OF AN HOUR AFTER THE MEAL

Patient	Number Samples	Cc N/10 NaOH High Pt	Cc N/10 NaOH Low Pt	Average	Average Deviation
M Hr	7	94	11	38	± 18.0
M Kn	7	82	41	62	± 11.5
M By	10	74	41	56	± 8.0
I Sn	14	51	33	43	± 3.5
E Kg	5	41	28	35	± 5.0
Normal Controls					
M Ma	11	63	35	51	± 7.0
C Te	9	69	58	64	± 3.0

The data have been further summarized in Table 1. It is evident that there is a wide variation in the acidity of successive samples taken from the same individual. For example, in the first subject (M Hr) the variation between the high point (94) and the low point (11) is 83. Such a striking divergence means that there is a gross error involved

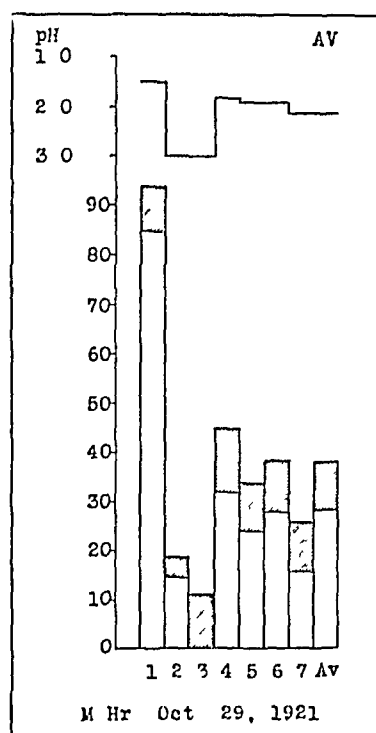


Fig. 1—The ordinates 0-90 represent cubic centimeters of tenth normal sodium hydroxide per 100 cc of gastric contents, pH , from 1.0 to 3.0 the hydrogen-ion concentration measured colorimetrically. The abscissae represent the number of samples taken, with the final column as an average of the preceding acidities. The colorless portion of each column represents the free acidity, while the light and the shaded portions together represent the total acidity.

in assuming any single sample as being representative of the total gastric contents. The last column marked "average deviation" brings this out mathematically. The average deviation is calculated in the following manner. The individual readings, such as 94, 19, 11, 45, 34, 38 and 26, are averaged, giving a mean of 38. The first reading (94)

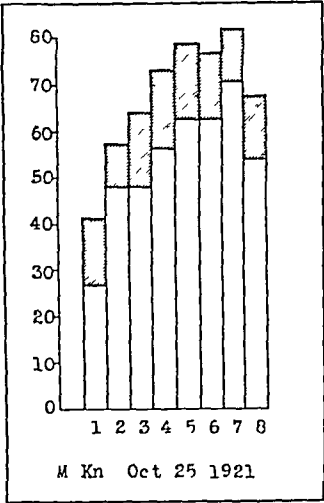


Fig 2

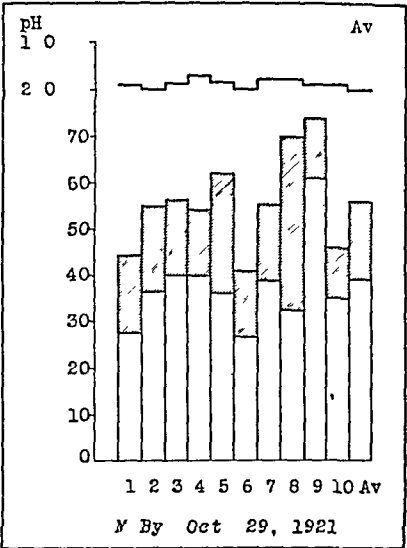


Fig 3

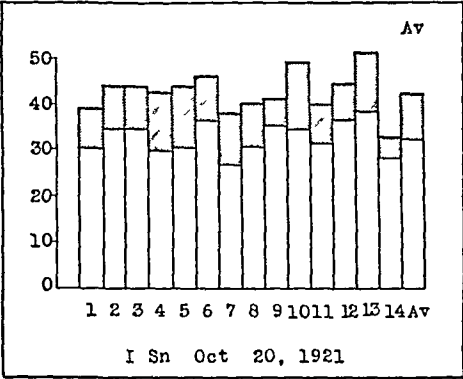


Fig 4

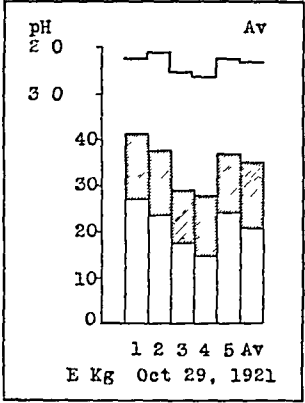


Fig 5

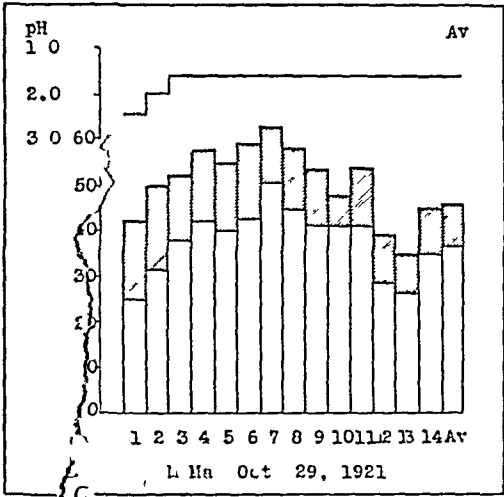


Fig 6

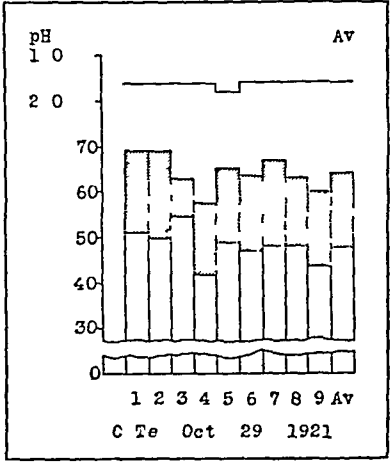


Fig 7

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deviates from the mean by 56, the second reading deviates by 19, and the third by 27—and so on. The sum of these deviations is 131. Dividing by the number of instances (7) one obtains the average deviation, which is ± 18 . In other words, considering the first subject, any single sample might be 18 more or 18 less than the average of all samples—which is virtually a range of uncertainty amounting to 36. Obviously, comparisons or conclusions based on such an uncertain method, when the experimental error is not calculated or taken cognizance of, are open to severe criticism.

It is scarcely necessary to discuss in detail the results obtained with the other subjects, for they merely emphasize in varying degree the points already established. Suffice it to say, that there was little difference between the normal controls and the psychotic patients having a similar acidity. In other words, it seems to be generally true that in subjects showing a fairly high gastric acidity one is more likely to find wider fluctuations than in those having a lower acidity. This may, perhaps, account for Gorham's findings, namely, that subjects with evidence of clinical disease, show wider fluctuations than the normal, and one may really expect that individuals without clinical evidence of disease who have a high acidity will also exhibit wide variations.

PART II

The above experiment explains, in part, the great variety of acidity curves obtainable by the fractional method of gastric analysis, and the fundamental errors involved in single determinations. The fraction obtained at any one moment cannot, therefore, be accepted as representative of the total gastric contents, for it is entirely dependent on the position of the tip of the tube in the stomach at the moment of withdrawal. Obviously, this position "is necessarily a constantly changing one, due, first, to the change of size and position of the stomach while emptying itself through the pylorus, and by aspiration, second, the shortening and lengthening of the stomach from gastric contraction, third, the peristaltic waves that tend to carry the tube toward the pylorus"². The experiment described in Part I, indicates that the gastric contents are not homogeneous, but the method involved is open to criticism on the ground that some little time is required to rapidly withdraw the successive samples, and that during such lapse of time the gastric acidity might actually be undergoing change. The following experiment, therefore, was designed not only to yield definite information concerning the acidity in different parts of the stomach at the same moment, but also to eliminate the lapse of time required in withdrawing several samples. The following procedure was carried out on three subjects, two psychotic patients and a normal individual. A Rehfuß tube was inserted to a depth of 50 cm (measured from the teeth)

Then a second Rehfuß tube was inserted to a depth of 45 cm, and, finally, a third Rehfuß tube was inserted to a depth of 40 cm. The gastric contents of each subject were removed simultaneously through all three tubes, by having the operators aspirate the contents at the same moment. The tubes were labeled and special care was taken to have each tube at the proper level before any gastric contents were removed. The standard Ewald meal was given and as usual, at fifteen minute intervals, samples were withdrawn, except that during these fractional analyses, three samples were aspirated simultaneously at the designated time. At the end of the analyses, each subject was given a glass of milk containing a small amount of bismuth subnitrate (15 grains) and a roentgenogram was taken to determine the relative posi-

TABLE 2—VARIATION IN ACIDITY OF THREE ALIQUOT FRACTIONS OF GASTRIC CONTENTS WITHDRAWN SIMULTANEOUSLY (M MCA)

Time, Hours	Total Acid	Average Average	± Deviation	Free Acid	Average Average	± Deviation	pH	Average Average	± Deviation
F C	45			33			1.6		
	22	34	± 12	9	21	± 12	1.6	1.6	± 0
¼	22			12			3.4		
	30			18			2.5		
	7	20	± 8	0	10	± 7	5.4	3.8	± 1.1
½	39			18			3.0		
	39			27			2.9		
	22	33	± 8	14	20	± 5	2.9	2.9	± 0
¾	69			38			2.2		
	56			30			2.4		
	28	51	± 15	18	29	± 7	2.1	2.2	± 0.1
1	74			51			1.7		
	63			42					
	21	53	± 21	14	36	± 14	2.5	2.1	± 0.4
1¼	73			49			1.8		
	68			46					
	37	59	± 15	29	41	± 8	1.8	1.8	± 0
1½	47			35			2.1		
	63			42			1.8		
	36	49	± 10	22	33	± 7	2.1	2.0	± 0.1
1¾	42			28			2.1		
	43			29			1.9		
	8	31	± 15	0	19	± 12	4.5	2.8	± 1.1
2	35			22			1.9		
	27	31	± 4	19	21	± 1	2.0	2.0	± 0

tions of the Rehfuß tubes maintained at a constant level. The acidity of the samples was determined in the usual manner by titration and colorimetric methods. The results of total acidity are graphically presented in Figures 8, 9 and 10, and summarized in Tables 2, 3 and 4.

In Table 2, may be found several points of interest. Chief among these are the wide variations occurring in the total or free acidity of the three fractions aspirated at any one time. Glancing down the second column marked "total acid" it is seen that at the one hour period there is a variation from 21 to 74, or an actual difference of 53. This is, perhaps, larger than the differences found at other periods, but since the one hour period is ordinarily of special interest, these figures are significant. In the third column is given the average of the three

TABLE 3—VARIATION IN ACIDITY OF THREE ALIQUOT FRACTIONS OF GASTRIC CONTENTS WITHDRAWN SIMULTANEOUSLY (M Hr)

Time, Hours	Total Acid	Average \pm Average Deviation	Free Acid	Average \pm Average Deviation	pH	Average \pm Average Deviation
F C	19		5		5.0	
	25	22 \pm 3	11	8 \pm 3	4.0	4.5 \pm 0.5
$\frac{1}{4}$	17		13			
	25		15		3.0	
	22	21 \pm 3	10	13 \pm 2	3.0	3.0 \pm 0
$\frac{1}{2}$	42		26		2.3	
	40		29		2.3	
	41	41 \pm 1	31	29 \pm 2	2.1	2.2 \pm 0.1
$\frac{3}{4}$	61		44		2.1	
	72		54		1.8	
	56	63 \pm 6	43	47 \pm 5	1.7	1.9 \pm 0.2
1	70		48		1.9	
	82		66		1.6	
	65	72 \pm 6	51	55 \pm 7	1.6	1.7 \pm 0.1
$1\frac{1}{4}$	79		60		1.7	
	71		56		1.7	
	62	71 \pm 6	48	55 \pm 4	1.7	1.7 \pm 0
$1\frac{1}{2}$	65		56		1.7	
	65		53		1.6	
	48	59 \pm 7	38	49 \pm 7	1.7	1.7 \pm 0
$1\frac{3}{4}$	80		71		1.7	
	58		47		1.7	
	51	63 \pm 11	43	54 \pm 12	1.7	1.7 \pm 0
2	74		64		1.6	
	61		53		1.6	
	61	65 \pm 6	54	57 \pm 5	1.7	1.6 \pm 0

TABLE 4—VARIATION IN ACIDITY OF THREE ALIQUOT FRACTIONS OF GASTRIC CONTENTS WITHDRAWN SIMULTANEOUSLY (M By)

Time, Hours	Total Acid	Average \pm Average Deviation	Free Acid	Average \pm Average Deviation	pH	Average \pm Average Deviation
F C	53		43		1.6	
	53		41		1.6	
	7	38 \pm 20	0	28 \pm 19	4.5	2.6 \pm 1.3
$\frac{1}{4}$	32		27		2.1	
	32		23		1.9	
	18	27 \pm 6	13	21 \pm 5	3.4	2.5 \pm 0.6
$\frac{1}{2}$	50		33		1.9	
	32		19		2.4	
	18	33 \pm 11	8	20 \pm 9	3.5	2.6 \pm 0.6
$\frac{3}{4}$	66		49		1.7	
	67		51		1.7	
	28	54 \pm 17	19	40 \pm 14	3.0	2.1 \pm 0.6
1	70		60		1.6	
	78		63		1.5	
	59	69 \pm 7	44	56 \pm 8	1.7	1.6 \pm 0.1
$1\frac{1}{4}$	78		64		1.6	
	82		73		1.6	
	75	75 \pm 3	57	65 \pm 6	1.6	1.6 \pm 0
$1\frac{1}{2}$	79		64		1.6	
	79		62		1.6	
	61	73 \pm 8	44	57 \pm 8	1.6	1.6 \pm 0
$1\frac{3}{4}$	75		61		1.6	
	78		66		1.6	
	51	68 \pm 11	37	55 \pm 12	1.6	1.6 \pm 0

fractions with the calculated average deviation. This shows conclusively how large the margin of uncertainty actually is, if one assumes any single reading as representative of the total gastric contents at any particular moment.

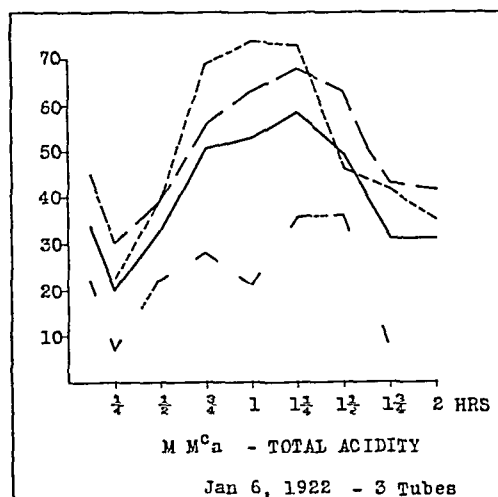


Fig 8—The ordinates 0-90 represent cubic centimeters of tenth normal sodium hydroxid per 100 c c of gastric contents, p_H from 10 to 30 the hydrogen ion concentration measured colorimetrically. The abscissae represent quarter hour intervals, and F C=fasting contents. The broken line represents the fraction taken from the tube at 50 cm, the dash and dot alternately, represents the fraction taken from the tube at 45 cm, the dash and several dots alternately, represents the fraction taken from the tube at 40 cm, while the solid line represents the average of the three fractions taken.

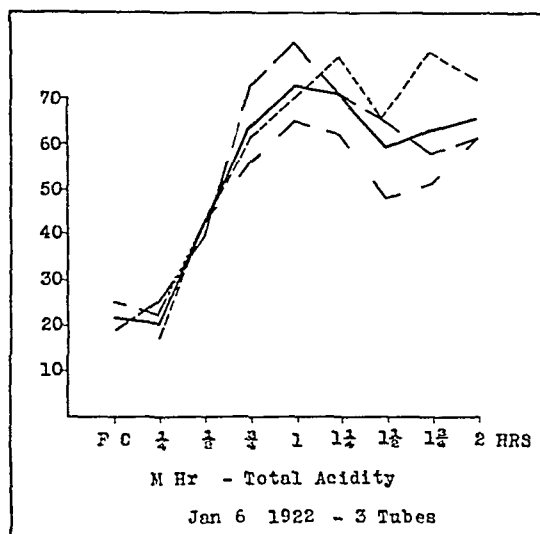


Fig 9

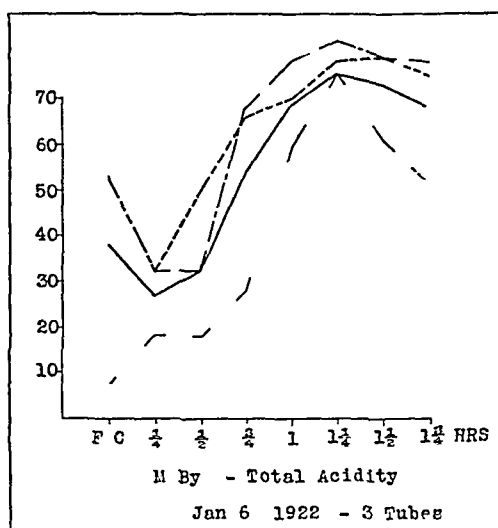


Fig 10

Figure 11 brings this point out even more strikingly. Usually, the higher the acidity, the wider the margin of uncertainty—a generalization already referred to in Part I. It is apparent from this graph that curves of various kinds could be drawn within the shaded area, from one designated by Rehfuess isosecretory to one designated hyposecretory.

This substantiates my earlier contention that a single determination by the Rehfuß fractional method of gastric analysis is not sufficiently valid on which to base a conclusion¹ It is clearly shown in the data here presented, that fractions taken from different parts of the stomach are not homogeneous in character, but differ widely in acidity The roentgenograms indicate the relative position of the tubes during the analyses One of these is shown in Figure 12

As might be expected, the free acidity values in Table 2, in general, run parallel to those obtained for total acidity But it is noteworthy that this does not hold true for p_H Here there is much closer agreement between the three fractions than when acidity is measured by titration This means that the buffer salts are of paramount importance in the measurement of true gastric acidity This lends further emphasis

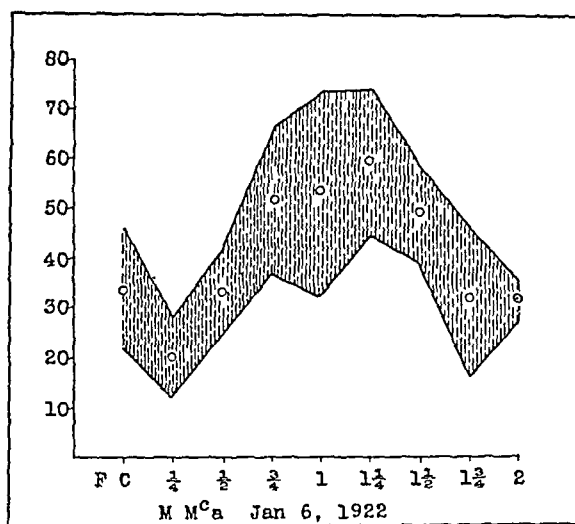


Fig 11 —The points in circles in the shaded area represent the average of the three fractions at the time indicated on the abscissae, while the shaded area above and below each point indicates the possible range into which the reading at that moment might fall

to the valuable work of Shohl⁵ and shows how misleading an index of gastric acidity a single titration may be

The other tables bring out in varying degree the facts already referred to and do not require a repetition of the discussion It is of interest, however, to note that the normal individual (M McA) exhibited even wider fluctuations in three fractions aspirated at the same time, than the two psychotic subjects (M Hr and M By), so that it cannot be said that the mental status has any particular bearing on the point at issue Naturally, various individuals would be expected to differ with regard to the homogeneity of their gastric contents, nevertheless, this experiment indicates that it is erroneous to assume that any such homogeneity exists

⁵ Shohl, A T Determination of the Acidity of Gastric Contents, Johns Hopkins Hosp Bull **31** 152 (May) 1920

In Tables 2, 3 and 4, a rather interesting phenomenon obtains. The fraction taken from the tube inserted at 40 cm is almost invariably lower in total and free acidity than the fractions taken at a depth of 45 or 50 cm. Furthermore, these samples were totally different in physical character—being of a much lighter color often, water-white, and containing lesser amounts of starch. This is to be expected from the work of Prym⁶ and Sick,⁷ who have shown that the acidity of the pyloric gastric contents varies considerably from the fundal portion, but their methods are not as conclusive as the one herein described, since

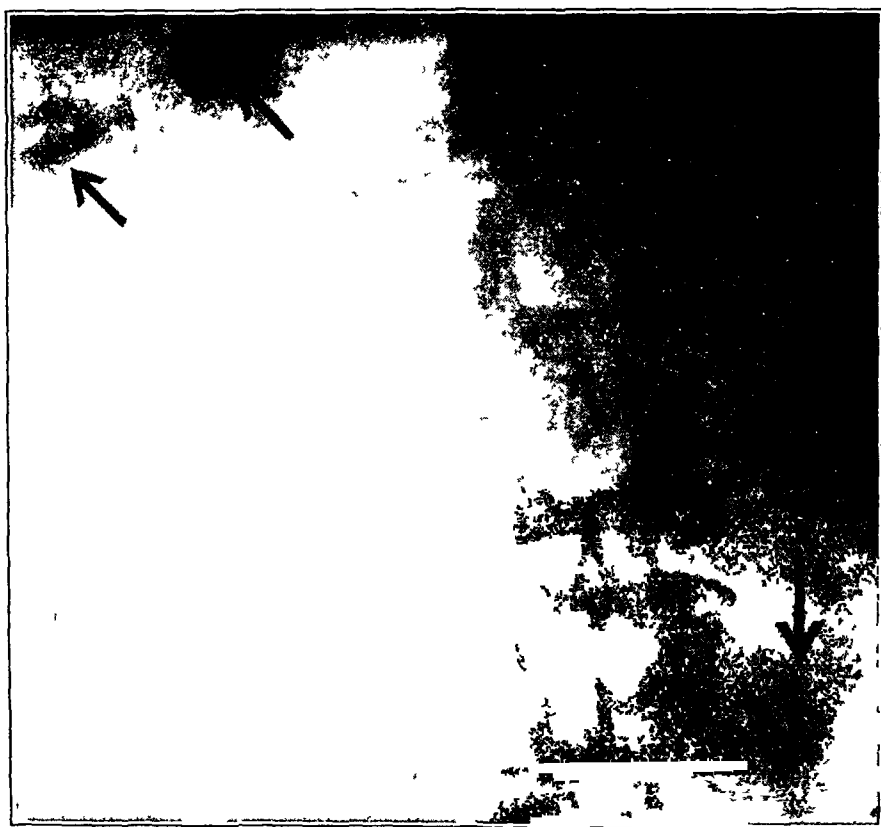


Fig 12—Relative position of Rehffuss tubes during fractional analysis with three tubes

they did not use more than one tube. Very little difference was found between fractions obtained at 45 and 50 cm, respectively. However, the fact that these two fractions are usually in close agreement indicates that in that region the stomach contents were, perhaps, of a more homogeneous character. In plotting the curves of the fractions taken at each level, a certain general similarity may be noted, despite the recrossing at numerous points. This might seem to indicate that if the level of the tube were kept constant, single determinations might yield a characteristic curve. However, the errors are too fundamental

6 Prym *Deutsch Arch f klin Med* 90 310 (June) 1907

7 Sick *Deutsch Arch f klin Med* 88 169 (Oct) 1906

to be thus lightly disregarded. For despite the similarity in curves, each curve has its peculiar margin of uncertainty, and thus the possibility of obtaining the characteristic curve would be seriously diminished. In other words, an average deviation of ± 12 for every sample, or practically 25 c.c., in the first subject, implies a wide margin of uncertainty.

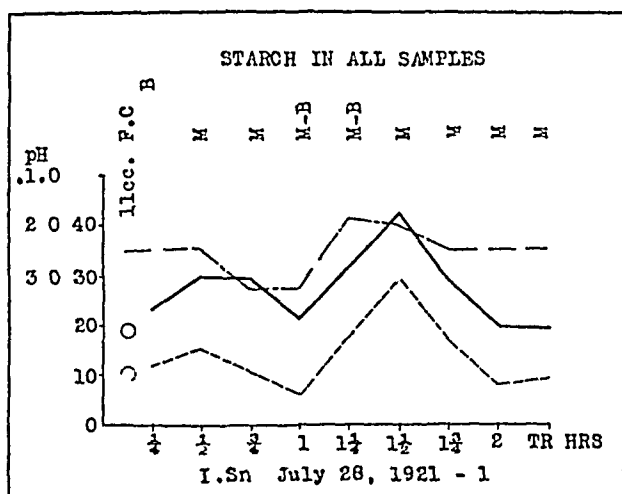


Fig 13

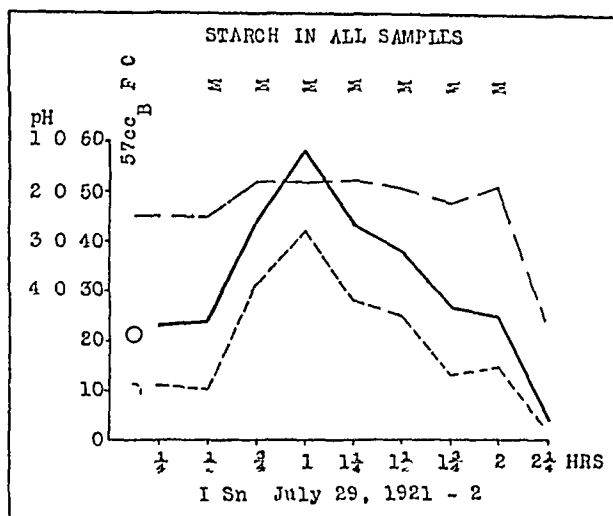


Fig 14

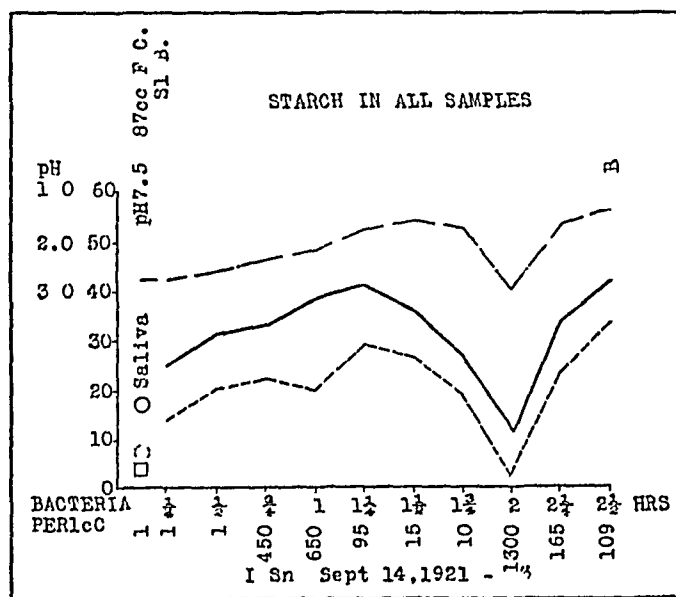


Fig 15

Figs 13, 14 and 15—Fractional analysis of stomach contents of a natural regurgitator

PART III

The problem of determining whether or not a small aliquot is truly representative of the total gastric contents was approached from still another aspect. Through the kindness of Dr William C Garvin, superintendent of Kings Park State Hospital, there was transferred to Ward's Island a psychotic patient who could be called "a natural regurgitator," i.e., one who could deliver his total gastric contents

at will, or on very slight stimulation of the palate. This patient gave a history of frequent vomiting after meals for which no adequate explanation could be given other than that it was an hysterical symptom. Since admission to Manhattan State Hospital, the vomiting has become relatively infrequent and generally occurs only after the patient has been visited. Several fractional gastric analyses were performed on him in the usual way (Figs 13, 14 and 15). Other than the relatively low acidity, there is little that is worthy of comment in Figures 13 and 15, while in Figure 14, the curve is typically isosecretory.

The power to regurgitate at will was utilized to study the homogeneity of the gastric contents. The subject was given the standard Ewald meal on several different days and instead of removing the contents by the fractional method, the total gastric contents were regurgitated on the first day after one-quarter hour, the next day after one-half hour, and so on, in such a way as to make it possible to plot a

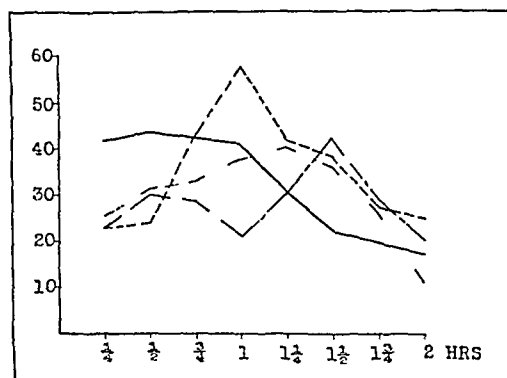


Fig 16—Homogeneity of gastric contents. Only the total acidity is shown. The solid line represents the total contents. The broken lines represent the fractional contents.

curve over the two-hour period, similar in scope to the usual fifteen minute fractions taken on the same day. A comparison of this curve with those obtained by the usual method is presented in Figure 16.

This curve representing the acidity of the total gastric contents has a higher initial acidity and a lower final acidity than that ordinarily found. Furthermore, instead of showing a gradual rise and decline, it is decidedly atypical in starting high and declining steadily. These peculiarities can scarcely be ascribed to the lapse of time between analyses, since the usual fractional method conducted at about the same intervals showed no marked changes, and the patient remained in about the same physical and mental condition so far as could be ascertained. While this method of conducting a gastric analysis is unusual, it gives a more adequate picture of the subject's gastric cycle of digestion than the routine method in vogue. Gorham² states that "the true fractional analysis necessitates the giving of successive test meals and extracting them at different periods."

A feature of some importance was added to the procedure described above, namely, an aliquot sample of 10 cc was taken by means of the Rehfuß tube immediately prior to the regurgitation of the total gastric contents, in fact, the removal of the Rehfuß tube in these instances stimulated "natural regurgitation" The comparison of each aliquot with the corresponding total contents is given in Table 5

In a subject having a rather low gastric acidity, as has already been pointed out, large differences could not be expected However, it is significant that there are noticeable differences This fact, together with the others mentioned in Parts 1 and 2, serves to complete the evidence against the usual technic of the Rehfuß method in which it is assumed that the aliquot withdrawn is representative of the total gastric contents, showing that such an assumption has little basis in fact

While these experiments may appear to be entirely destructive in character, nevertheless, certain constructive points have been estab-

TABLE 5—COMPARISON OF ALIQUOT WITH CORRESPONDING TOTAL GASTRIC CONTENTS OBTAINED BY "NATURAL REGURGITATION"

Time	Total Acidity in Cc N/10 NaOH	
	Aliquot	Total Contents
1 hour	49	41
1½ hours	37	22*
2 hours	22	17

* Some bile present

lished First and foremost, in using the Rehfuß method, it is essential to repeat the analysis until a satisfactory agreement in curves is obtained Second, the tube should be kept at a constant level This can easily be accomplished by fastening the tube to the cheek by means of a strip of surgeon's adhesive tape Third, the aliquot fractions should be as large as possible Fourth, the subject should expectorate freely, swallowing as little saliva as possible Finally, the acidity should be measured in terms of hydrogen ion and buffer salts, and not by the inaccurate titration method in common usage

SUMMARY

1 A wide variation was found in the acidity of 10 cc fractions withdrawn in rapid succession by means of the Rehfuß tube three-quarters of an hour after the test meal was ingested This was more noticeable in subjects having high rather than low gastric acidity

2 By inserting three Rehfuß tubes in one individual and aspirating the fractions simultaneously at fifteen minute intervals, it was found that there was considerable variation of acidity in different parts of the stomach at the same moment Roentgenograms established the relative position of the tubes

3 From these data it is shown that widely divergent curves of acidity may be plotted which depend entirely on the experimental error of the method and not on the subject's gastric condition

4 The inadequacy of the titration method and the importance of hydrogen ions and buffer salts in measuring gastric acidity is indicated

5 By comparing the periodic "natural regurgitation" of total gastric contents with the fractions ordinarily obtained by the Rehfuß method, discrepancies are noted

6 Results obtained by the Rehfuß method may be more validly interpreted if (a) the analysis is repeated until a satisfactory agreement in curves is obtained, (b) the tube is kept at a constant level, (c) aliquot fractions are large, (d) little saliva is swallowed, (e) acidity is measured in terms of hydrogen ion and buffer salts

CONCLUSION

Aliquot fractions obtained by the Rehfuß method of gastric analysis cannot be assumed to represent accurately the total gastric contents

I am indebted to the individuals who made these experiments possible and to the members of the staff for their generous assistance. Particular thanks are due Dr C O Cheney for his many valuable suggestions and help on the wards, and to Mr E J Kennedy for his efficient and painstaking work in the laboratory

BOOK REVIEWS

HAY FEVER AND ASTHMA WILLIAM SCHEPPEGRELL Philadelphia and New York Lea & Febiger, 1922

This text, pleasingly concise, presents the etiologic relationship of plant pollen to hay-fever, and mentions for each state of the United States the particular plant pollen seasonally associated with hay-fever. Although the title implies a discussion of asthma, very little mention of this disease is made in the text. The preventive control of hay-fever, and its treatment are presented adequately. The book is a useful guide in determining the offending pollen, and in the treatment of hay-fever patients.

MANUAL OF CLINICAL LABORATORY METHODS C L CUMMER Philadelphia and New York Lea & Febiger, 1922

This is a convenient laboratory manual, systematically presented, and adequately describes the present methods essential for good clinical laboratory work. That portion of the text concerned with the blood includes directions for the usual cytologic examinations, serologic and bacteriologic tests, and also for the quantitative estimation of many of the chemical substances of the blood, such as sugar, urea, total nonprotein nitrogen, creatinin, uric acid, alkaline reserve, chlorids, and oxygen. There are chapters describing the methods for urine analysis, the examination of gastric and duodenal contents, of feces, sputum, body fluids, and also for bacteriologic examinations. This book meets the needs of any clinical laboratory worker, and of physicians who desire interpretation of laboratory reports.

BACTERIOLOGY GENERAL PATHOLOGICAL, INTESTINAL A I KENDALL Philadelphia and New York Lea & Febiger, 1921

Kendall's revised bacteriology (Ed 2) needs little introduction as a reference text to advanced students of bacteriology. As a text for courses in bacteriology to medical students and to students of general bacteriology, it deserves favorable consideration. The revision has brought into the text discussion of certain pathogenic bacteria which during the war became especially important. Entire sections of the book are rewritten and extensive changes or additions made to nearly every chapter. A section discussing gastro-intestinal bacteriology is a distinctive feature of this book.

THE VITAMINS By H C SHERMAN, Professor of Food Chemistry, Columbia University, and S L SMITH, Specialist in Biological and Food Chemistry, U S Department of Agriculture New York The Chemical Catalog Company, 1922

This book combines scientific accuracy with simple diction, so that it can be studied with ease and profit by the educated layman and by the doctor who left school before the recent discoveries in the vitamin field of nutrition. The first chapter contains an excellent historical review of the development of knowledge of the vitamins and their rôle in health and disease. The following three chapters deal in detail with the antineuritic, the antiscorbutic, and the fat soluble vitamins, respectively. The final chapter deals with the very important subject of vitamins in our ordinary foods. There are good subject and authors' indexes, and a bibliography of 1,000 titles, for those who have the time and the inclination to consult the original publications. The authors are men of recognized attainment in the field of food and nutrition.

The book is one of the best, if not the best, written on the timely subject of the vitamins. It will help to allay the hysteria that now threatens to develop on the subject of the vitamins and vitamin deficiency diseases, a hysteria brought on by baseless claims of vitamin deficiency in our common food, and generously nursed by vitamin proprietary purveyors.

NERVE EXHAUSTION By MAURICE CRAIG, C B E, M D (CANTAB),
FRCP (LOND), Physician for and Lecturer in Psychological Medicine,
Guy's Hospital. Late Examiner in Diploma for Psychological Medicine,
Cambridge University. 148 pages. Philadelphia, Lea & Febiger. 1922.

The outstanding features of this book are common sense and simplicity. In spite of his undoubted possession of perfect knowledge of modern psychopathologic lingo, the author expresses his ideas in plain English, even avoiding such terms as neurasthenia and psychasthenia. Nerve exhaustion is discussed under five principal headings: causation, symptomatology, sleeplessness, diagnosis and prognosis, treatment. According to Craig, there is nothing haphazard about fatigue and it is our duty to discover the rules governing its occurrence. His discussion of the hypersensitive, precarious child and its management if read not only by physicians, but by teachers and educated parents would be most helpful in the prevention of nervous invalidism. His ideas on gastro-intestinal hygiene may sound a little revolutionary to most Americans with whom "regulation" of the bowels has almost become a national duty. We are told that a tendency to looseness of the bowels is much more harmful to the nervous system than constipation. He does admit that "colitis" is usually associated with constipation, but adds that it is common in highly-strung persons and that "it is wise to focus the treatment as little as possible upon the condition, as the psychical effect of doing so may be both great and lasting." In commenting on the comparative frequency of nervous exhaustion following surgical operations he deplores the tendency to unnecessarily violent purging just before operations. The author evidently has carefully studied the Freudian Philosophy—and finds it wanting. He does not believe that sexual conflicts and suppressions are of necessity the cause of psychoneuroses. He is also impressed with the harm frequently done to patients by psychoanalytic treatment. Altogether we can heartily recommend this book to physicians no matter what line of work they may follow, as it will enable them to understand better the one subject common to general practitioners and specialists alike—the patient himself.

THE ABSORPTION OF DIGITALIS IN MAN *

CARY EGGLESTON, M D, AND JOHN WYCKOFF, M D

NEW YORK

Different samples of digitalis vary widely in their therapeutic effectiveness when given orally to man, and the development of biologic methods for the assay of digitalis shows that different specimens of the drug also vary greatly in activity on the animal heart, the most active being at least three times as potent as the weakest specimen. This wide divergence in activity was believed to account for the observed variability in the therapeutic efficiency of the drug, and it was hoped that the general adoption of one or another method of biologic assay would eliminate the uncertainty of therapeutic effects. While this has not been accomplished, it is now unusual for the therapist to find a very weak specimen of digitalis, and it is exceptional for the most active specimen to exceed the weakest by more than 50 per cent. The average high grade digitalis of the present time is generally a fairly trustworthy therapeutic agent, but there still remains a considerable range in activity of the drug in man and several striking instances of the therapeutic failure of presumably excellent samples have come to notice.

The literature on the absorption of digitalis in man is meager, but it has been shown¹ that the galenical preparations of digitalis are absorbed from the human alimentary canal with sufficient uniformity to permit the establishment of an average total therapeutic requirement of the drug. The validity of this average requirement has been confirmed by several investigators,² and for samples of digitalis from various sources and of widely divergent activity. It was also shown¹ that both digitalis and digitoxin are usually absorbed promptly from the digestive tract, but no attempt was made to determine the exact rate of their absorption, although the evidence indicated that it was essentially completed within about six hours after administration.

* Read before the New York Academy of Medicine, Jan 19, 1922

* From the Department of Pharmacology, Cornell University Medical College, The Second Medical (Cornell) Division and The Third (New York University) Division of Bellevue Hospital

1 Eggleston, Cary. Digitalis Dosage, *Arch Int Med* **16** 1 (July) 1915

2 Robinson, G Canby. Rapidity and Persistence of the Action of Digitalis on Hearts Showing Auricular Fibrillation, *Am J M Sc* **159** 121, 1920
White, S Marx, and Morris, R Edwin. The Eggleston Method of Administering Digitalis, *Arch Int Med* **21** 740 (June) 1918

Cohn, Fraser and Jamieson³ pointed out the importance of a flattening or inversion of the T wave of the electrocardiogram as an early sign of the action of digitalis on the human heart. Cohn⁴ and White and Sattler⁵ have emphasized the constancy and very early appearance of a prolongation of the conduction time following the therapeutic use of digitalis. Pardee⁶ has confirmed the importance of the lowering of the T wave as an evidence of the action of digitalis on the heart and has employed it in an investigation of the rate of the absorption of the drug by man. He gave doses of one half to two minims of the tincture per pound of the patient's body weight to nine patients and found that the action on the heart muscle as shown by the change in the T wave began in from two to four hours and reached its maximum at the sixth or seventh hour. He says that the beginning change in the T wave was noticed by the second hour in three patients, but that it might have been observed in others had more records been taken at that hour.

Robinson² studied the action of single large doses of the tincture of digitalis in a series of carefully controlled cases with auricular fibrillation and observed that the first effects in sixteen cases made their appearance in from two to five hours after the administration of the drug by mouth. He employed as the criterion of beginning action the appearance of definite reduction in the ventricular rate, which progressed on subsequent observation. Although the magnitude of the dose, the type of patient, and the index of digitalis absorption and action on the heart mechanism were all different from those in Pardee's series, Robinson's observations confirm those of Pardee with reference to the rapidity and comparative uniformity of absorption of digitalis from the human alimentary canal.

The observations reviewed are not in harmony with those recorded by Wedd⁷. He employed two assayed preparations of the tincture (cat method) and gave daily doses of from 8 to 12 c c, usually 10 c c. One tincture, having a cat unit of 111 mg, was given to five patients as follows. The first patient took 72 c c, or 0.52 cat unit per pound,⁸ with

3 Cohn, A. E., Fraser, F. R., and Jamieson, R. A. The Influence of Digitalis on the T Wave of the Human Electrocardiogram, *J. Exper. Med.* **21** 593, 1915.

4 Cohn, A. E. Clinical and Electrocardiographic Studies on the Action of Digitalis, *J. A. M. A.* **65** 1527 (Oct. 30) 1915.

5 White, Paul D., and Sattler, R. R. Effect of Digitalis on the Normal Human Electrocardiogram, *J. Exper. Med.* **23** 613, 1916.

6 Pardee, H. E. B. Rate of Absorption of Digitalis from Gastro-Intestinal Tract, *J. A. M. A.* **75** 1258 (Nov. 6) 1920. Principles of the New Method of Administering Digitalis, *New York M. J.* **110** 1064, 1919.

7 Wedd, Alfred M. Observations on the Clinical Pharmacology of Digitalis, *Johns Hopkins Hosp. Bull.* **30** 131, 1919.

8 All statements of dose in terms of cat unit refer to the fraction of a cat unit per pound of the patient's body weight.

the production of nothing but slowing of the pulse while at rest in bed. The second patient took 115 c c, without clinical effect, or a total of 0.80 cat unit. The third patient took 0.67 cat unit, or 101 c c, with very slight slowing and no toxic effects. The fourth patient showed marked reduction in the pulse rate, but no toxic symptoms after a total of 137 c c, or 0.87 cat unit, and the fifth patient showed similar effects after 149 c c, or 0.95 cat unit. Although this sample of digitalis was of approximately average activity on the cat, it is evident that it was therapeutically unsatisfactory, either due to poor absorption or to unusually rapid elimination.

The second tincture Wedd used was 30 per cent more active on the cat than the first and gave better therapeutic response, although the range of total dose required varied within wide limits. Some patients took from two to nearly four times the average total dose, as determined by Wedd in twenty-two patients, without marked intoxication. Wedd concludes that the inefficiency of the first tincture was due to delayed absorption from the alimentary tract, the cause of which is unknown. He says, as a result of his use of these two tinctures in twenty-seven patients, "It is evident, however, that biologic standardization showing approximation to theoretic strength is no guarantee of the clinical efficiency of a given preparation of the drug. Individual power of absorption for a given tincture appeared to be quite uniform, so variation in toxic dosage is due to variation in individual tolerance for the drug." He says, further, "No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered." We will return to these statements subsequently.

Wedd also found that the first definite effect of digitalis on the heart was a lowering or inversion of the T wave of the electrocardiogram. In one patient this effect began after 16 c c, of the first tincture was taken, and in the remaining four an average of 34 c c was required before any definite change could be detected. The second tincture showed beginning changes in the T wave after 10 c c, or less in most cases, indicating that the first tincture was absorbed much less rapidly than the second. Several other instances of specimens which were poorly absorbed and therapeutically unsatisfactory have also come to our attention and have been referred to elsewhere.⁹

Prior to the appearance of Wedd's paper Hatcher¹⁰ had been studying the extraction of digitalis with a view to obtaining a satis-

⁹ Eggleston, Cary. The Absorption of a Digitalis Body, *J. A. M. A.* **75** 463 (Aug. 14) 1920.

¹⁰ Hatcher, R. A. Some Observations on the Pharmacology of a Digitalis Body, *J. A. M. A.* **75** 460 (Aug. 14) 1920. Standardization of Digitalis, *J. Am. Pharm. Assn.* **8** 913, 1919.

factory preparation for intravenous use and had found that the active principles of the drug were readily separable into two fractions by extraction of the aqueous extract with chloroform. He found that the fraction which was soluble in chloroform bore close resemblances to digitoxin both chemically and pharmacologically and was readily absorbed from the alimentary tract of the cat. The water soluble remainder, or the chloroform insoluble fraction, on the other hand, resembled digitalein pharmacologically and was both poorly and irregularly absorbed from the alimentary canal of the cat. Both fractions, however, when tested pharmacologically produced typical digitalis actions. Hatcher found that the relative proportions of these two fractions varied widely in different samples of digitalis, although technical difficulties have so far prevented the elaboration of a satisfactory method for the accurate quantitative determination of the relative proportion of the fractions. Nevertheless, several therapeutically unsatisfactory samples of digitalis were examined and found to contain decidedly smaller relative proportions of the chloroform soluble fraction than were present in the average specimens. This would account for the poor absorption of these specimens by man, provided that in man the two fractions show differences in absorbability similar to those shown in the cat.

The findings reviewed show (1) that most high grade digitalis commercially available is absorbed from the alimentary tract of man with a fair degree of uniformity—at least sufficient to permit the establishment of a satisfactory average therapeutic requirement, (2) that a considerable proportion of a single large dose may be absorbed within from two to four hours, (3) that the absorption of a single dose is generally completed within from six to eight hours, (4) that specimens of digitalis are sometimes encountered which, while biologically of satisfactory activity, are therapeutically unsatisfactory apparently on account of slow and poor absorption, and finally, (5) that digitalis is easily separable into a chloroform soluble fraction which is readily absorbed from the digestive tract of the cat and a chloroform insoluble portion which is slowly and poorly absorbed. The last finding suggests an explanation of the unsatisfactory clinical results yielded by some samples of digitalis. Therefore it seemed advisable to undertake an extensive reinvestigation of the whole matter of digitalis absorption in man, especially in view of the observations of Hatcher¹⁰ on the two fractions obtainable from the drug. This was begun in 1919 and a preliminary report was published in 1920⁹ in which evidence was obtained as to the relative absorbability in man of the chloroform soluble and the chloroform insoluble fractions. Certain of the observations presented in that report will be reviewed in connection with the discussion of the results of the investigations about to be detailed.

At present we desire to emphasize the fact that the chloroform soluble fraction was shown to be absorbed from the digestive tract of man at least as rapidly as are the best tinctures, and its absorption was shown to be more nearly uniform than that of different tinctures. The chloroform insoluble fraction was shown to be absorbed very poorly by man. The similarity in the behavior of the cat and man toward the absorption of these two fractions was thus established. Finally, a working average dose of the chloroform soluble fraction was established which enabled us to proceed at once to the determination of the rate of its absorption after the oral administration of large single doses, or of large doses given in two or three fractions at short intervals of time.

METHODS AND SCOPE OF INVESTIGATIONS

Patients suffering from various degrees of cardiac failure, and a few without clinical evidences of failure, were selected to exclude all who had been receiving digitalis in any form or in any dose within two weeks of the beginning of observation. All patients were placed on an arbitrary fixed regimen which included confinement to bed with the head elevated, a simple semisolid diet, and when edema or anasarca was present the daily fluid intake was limited to between 1,000 and 1,500 c c, except when the Karrel diet was deemed necessary. The patients were weighed before the administration of digitalis and at intervals during and after its administration, an effort being made in every patient with edema to secure his weight after the disappearance of all edematous fluid. In patients with edema the initial dose was calculated on the body weight after deduction of the estimated weight of edema fluid. Whenever the patient's condition permitted, he was given a period of rest in bed on the fixed regimen for from three to five days before the digitalis was administered. Whatever dietary prescription was adopted in any patient was maintained until the period of initial observation of the effects of digitalis was completed. Occasional doses of codein, morphin or a simple laxative were required, but aside from these no other drug therapy was permitted.

All patients were examined by one or both of us at frequent intervals before and during the course of treatment and the patient's condition was described as accurately as possible. At least one control electrocardiogram was made of all but seven patients shortly before the administration of digitalis. Within from one half to three hours following the initial dose of digitalis, electrocardiograms were taken hourly, with few exceptions, for from four to seven hours.

Digitalis In order to make comparisons we employed four different lots of the chloroform soluble fraction, which we have termed for convenience, "purified tincture." These were prepared and supplied to us

by Dr Robert A Hatcher in the form of a solution of the chloroform soluble substance in 60 per cent alcohol of such strength that 1 cc of the purified tincture represented one cat unit in activity These purified tinctures were derived from many different specimens of digitalis, as follows P T 3-18-20 consisted of a repurified mixture of many specimens of the purified chloroformic extract prepared in different ways from a variety of specimens of digitalis leaf P T 7-23-20 was prepared from the powdered leaf from which the galenical tincture H was made P T 8-19-20 was also prepared from the same leaf as the preceding, but efforts made to repurify this specimen yielded one which was weaker than the ordinary purified—an unusual result P T 12-30-20 was a mixture of twenty-five different specimens which were purified with a view to the removal of traces of chlorophyll, volatile oil and of saponin

For comparison with these we used two samples of galenical tincture of digitalis, S, being a specimen which in the hands of others had proved therapeutically unsatisfactory Tincture H was made from a leaf which on examination had yielded a relatively very low proportion of the chloroform soluble fraction Both specimens were biologically of good activity

Preparation and Standardization of Purified Tincture The active substance of the purified tincture is obtained in the simplest way by infusing the powdered digitalis with cold water, shaking this with chloroform, distilling the chloroform, washing the residue with petroleum ether, and drying¹⁰ The yield by this method is smaller and a larger one can be obtained by infusing the powdered digitalis with from seventy-five to 100 parts of hot water, shaking the infusion several times with chloroform, washing the chloroform with distilled water, and proceeding as described

Since the preliminary report Hatcher¹⁰ has found that the chloroform soluble extract contains a large proportion of a digitalis body which is very rapidly eliminated after intravenous injection into the cat, and which does not correspond to any digitalis body hitherto described Its action is so fleeting that it probably does not participate in the therapeutic action of the purified tincture of digitalis, though it does participate in the action following intravenous injection For clinical use by oral administration the purified tincture is standardized as follows

About 75 per cent of that dose which causes death in the cat when injected intravenously at once is administered intravenously to each of several animals After an interval of three hours (during which practically all of the rapidly eliminated substance is excreted) the amount of ouabain required to cause death by intravenous injection is determined The difference between the amount of ouabain required in such an experiment and that required to kill a normal animal of the same weight

is equivalent to that portion of the previously injected purified tincture, the action of which persists. The following calculation illustrates the method. A cat weighing 2 kg. received 1.5 cc of the purified tincture intravenously, after three hours it required 50 per cent of the average fatal dose of ouabain to cause death, hence the action of 50 per cent of the average fatal dose of the purified tincture persisted. Since 1.5 cc represented 50 per cent of the fatal dose by this method, it follows that 3 cc, or 1.5 cc per kg of weight, would represent 100 per cent of the fatal dose in terms of the substance having a persistent action. Therefore 1.5 cc of this purified tincture would represent one cat unit as determined in this manner, which Hatcher terms for convenience the "slow combined ouabain method" of assay.

The cat unit of the purified tinctures standardized by the slow combined ouabain method, therefore, represents the activity of that portion only which has a persisting action, the rapidly eliminated portion having been excluded from consideration. All of the purified tinctures used in the present study were standardized in this manner.

REPORT OF CASE

The following abstract of a typical case will serve to illustrate the method of study in detail.

G. F. (Fig. 1), male, aged 56, bartender, was admitted to the hospital April 2, 1921. Discharged April 14—improved.

Chief Complaints on Admission Shortness of breath, cough, and swelling of legs.

Family History Father died of heart disease at 76.

Past History Yellow fever twenty-one years ago, acute arthritis in right shoulder and both elbows seven years ago. Denies venereal infection.

Habits Has used alcohol to excess, especially during the past two years. Drank half a gallon of coffee daily until two months ago. Smokes heavily.

Present Illness—This began gradually eight months ago with dyspnea on exertion only. This became worse, and dyspneic attacks began to occur without exercise, usually at night. For the past six weeks he has suffered from nocturnal orthopnea. With the increasing severity of the dyspnea there has developed a sensation of fluttering about the heart. His legs began to swell six weeks ago. The conditions have all grown gradually worse up to time of admission.

Physical Examination—Patient is a large man, very cyanotic, dyspneic and orthopneic. Veins of neck not visibly distended. Lungs show signs of congestion at both bases. Heart. Apex beat not visible, point of maximum intensity in sixth intercostal space 12 cm. to left of midline. Dulness extends 4 cm. to right of sternal margin in second intercostal space. No murmurs are present. Heart sounds are of poor quality, and the rhythm is totally irregular. Rate at apex—142. Pulse. Radial arteries sclerosed, pulse totally irregular, rate 120. Abdomen. Adipose and pendulous, no ascites detected. Liver edge palpable 5 cm. below free border of ribs, tender but not pulsating. Marked edema of legs and scrotum.

Laboratory Examination—Blood Wassermann test negative. Urine. Trace of albumin and a few casts.

Treatment—Patient was confined to bed and provided with a back rest. The diet was semisolid with the fluid intake restricted to 1,000 cc per twenty-four hours. A single dose of purified tincture of digitalis 12-30-20 amounting to 115 cc was given at 12 45 p m, April 5.

Clinical Course—April 4. With rest in bed and restricted fluid intake patient's edema has diminished. He is still dyspneic and orthopneic and some edema persists in legs.

April 5. 12 noon. Patient's condition practically as on April 4, says he feels a little better. Liver edge as before. Still some edema of legs and some dyspnea and orthopnea.

April 5. 5 30 p m. Patient says he feels much better. He is less dyspneic and is able to lie nearly flat without discomfort. There is no nausea or vomiting.

April 6. There is no pulse deficit today. His general condition is much improved. Is able to lie flat.

April 7. Liver is no longer definitely palpable, but there is still some tenderness in right hypochondrium. Edema has entirely disappeared.

From this time on patient continued to improve until discharged. Figure 1 shows some of the events in the course of his treatment.

More than seventy patients were studied in the manner just described before the investigation was brought to a close. No analysis of the results was undertaken until this time and it was found that, for one or another reason, usually some omission of data, a number of the records had to be discarded. The records of fifty-two courses of administration to fifty-one patients remained, in which the data were sufficiently complete, and it is on these that the present paper is based. Space does not permit the presentation, even in brief abstract, of the records and we have resorted instead to the preparation of several tables in which the details are presented in a form more readily available for study and analysis. In every instance we analyzed the electrocardiograms without knowing the preparation of digitalis which the patient received, the dose given or the time of its administration in order to avoid any unconscious bias, especially in view of the fact that our preliminary work had indicated a more rapid rate of absorption for the purified tinctures than for the galenical.

Tables 1 and 2 show the nature of the earliest effect which was observed following the administration of the digitalis, the dose which produced this effect, expressed in terms of a fraction of a cat unit per pound of the patient's body weight, the time in hours at which the first effect was manifested, measured from the time of the administration of the drug, the nature of the phenomena evident at the time of maximal therapeutic effects, and the dose and time at which these developed just as in the case of the earliest effects. When more than one dose of digitalis was administered during the period of observation covered in the table the time is taken from the administration of the first dose. In all of the patients receiving the purified tinctures the first effects followed a single dose, and while this was also true in many of those receiving a galenical tincture, in some two or more doses were administered before any effects were demonstrable. Table 1 includes

only those patients showing sinus rhythm, while the same types of observations are presented in Table 2 for the group of patients having auricular fibrillation

It will be noted that we have not limited ourselves to any single phenomenon, or to any small group of phenomena, for the determination

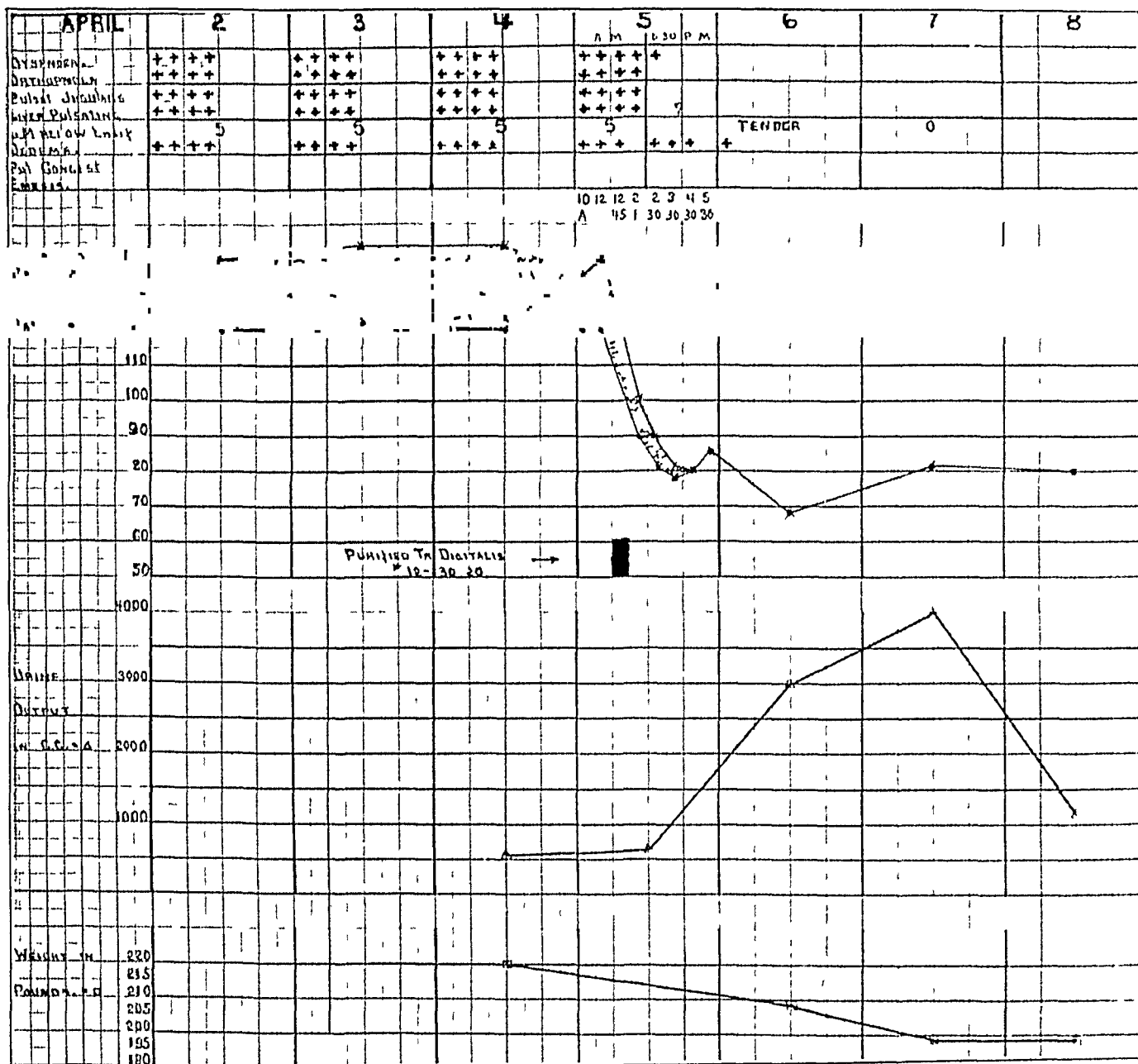


Fig 1—Chart showing course of events in patient 42, with auricular fibrillation. At 12 45 p m, April 5, 1921, a single dose of 115 cc of purified tincture of digitalis 12-30-20 was administered—indicated by the black square on the chart

of the onset of earliest digitalis effects, but instead have recorded the first definite digitalis effect which made its appearance. This was done because it was our object to determine the very earliest evidence of

digitalis action as an index of the rate of the absorption of the drug, and since the earliest manifestation is not always the same we felt that the adoption of a limited number of criteria would lead to erroneous

TABLE 1—SHOWING THE INITIAL AND THE FULL THERAPEUTIC EFFECTS PRODUCED WITH THE DOSES PRODUCING THEM AND THE TIMES OF THEIR APPEARANCE, FOR PATIENTS WITH SINUS RHYTHM

No	Initial Effects	Cat Units per Lb	Time in Hours	Full Therapeutic Effects	Cat Units per Lb	Time in Hours
Purified Tincture Digitalis No 3-18-20						
1	Lowered T2	± 0.066	1	Vomiting	0.150	42
2	Lowered T2 and T3	0.067	± 2	Slowing, T2 diphasic, premature contract	0.088	4
3	Slight slowing	0.064	1	Increased P R	0.095	4
4	Increased P R	0.056	1	Slowing, diphasic T2, increased P R	0.056	3
5	Lowered T2	0.059	1	Slowing, diphasic T2, increased P R	0.059	5
6	Slight slowing	0.061	1	Clinical improvement	0.104	48
7	Slight slowing	0.061	1	No record		
8	No preliminary observation			Lowered T2, increased P R	0.073	5
Purified Tincture Digitalis No 12-30-20						
9	Lowered T1	0.051	1	No further effects		
10	Lowered T2	0.059	1	Lowered T2, clinical improve ment	0.059	5
Purified Tincture Digitalis No 7-23-20						
11	Slowing, lowered T2	0.051	1	Marked slowing, T2 diphasic, in creased P R	0.092	5
12	Slowing increased P R	0.040	2	Emesis	0.073	5
13	Lowered T2 increased P R	0.045	1	Slight nausea, further slowing, inversion T2	0.090	5
14	Slowing, lowered T2	0.052	1	Marked slowing removal of pre mature contract	0.085	4
Purified Tincture Digitalis No 8-19-20						
15	Lowered T2	0.046	1	Diphasic T2, dropped beats, slowing	0.070	4½
16	Lowered T2, slowing	0.050	1	Inverted T2, auricular fibrillation ventricular paroxysm, tachycardia, coupled rhythm, nausea, vomiting	0.082	5+
Tincture Digitalis No S						
17	Coupled rhythm, premature contract	± 0.118	7	Slowing	0.253	50
18	Increased P R, lowered T2	0.118	5	Single dose		
19	Lowered T2, premature contract	0.117	2½	Nausea	0.173	18
20	Lowered T2	0.122	1	Vomiting, marked clinical improvement diuresis, slowing	0.390	84
21	Slowing, lowered T2	0.100	5	Slowing, lowered T2, slight clinical improvement	0.170	26
Tincture Digitalis No H						
22	Slight slowing lowered T2, increased P R	0.060	2	Nausea, lowered T2, increased P R	0.144	49
23	Increased P R, lowered T2	0.057	3	Emesis, slowing, T2 diphasic increased P R	0.260	74
24	Slowing, lowered T2	0.078	3	Slowing premature contract, clinical improvement	0.260	42
25	Lowered T2 slowing, increased P R	0.100	3	Further slowing, increased P R, lowered T2	0.100	7

results Where two or more phenomena appeared simultaneously they are recorded Slowing was usually determined from the electrocardiograms rather than from counts of the pulse or heart beat

The cases are numbered serially through Tables 1 and 2 and the numbers correspond to those appearing in subsequent tables

In Cases 2 and 8, in which no control electrocardiograms were taken, the lowering of the T wave recorded was determined by comparison with the first record taken, which was obtained in both instances one hour after the initial dose of digitalis

ANALYSIS OF OBSERVATIONS

Definite initial effects of digitalis were recorded in thirty-three cases receiving the purified preparations, fifteen being patients with the sinus rhythm, and eighteen with auricular fibrillation. These are shown in

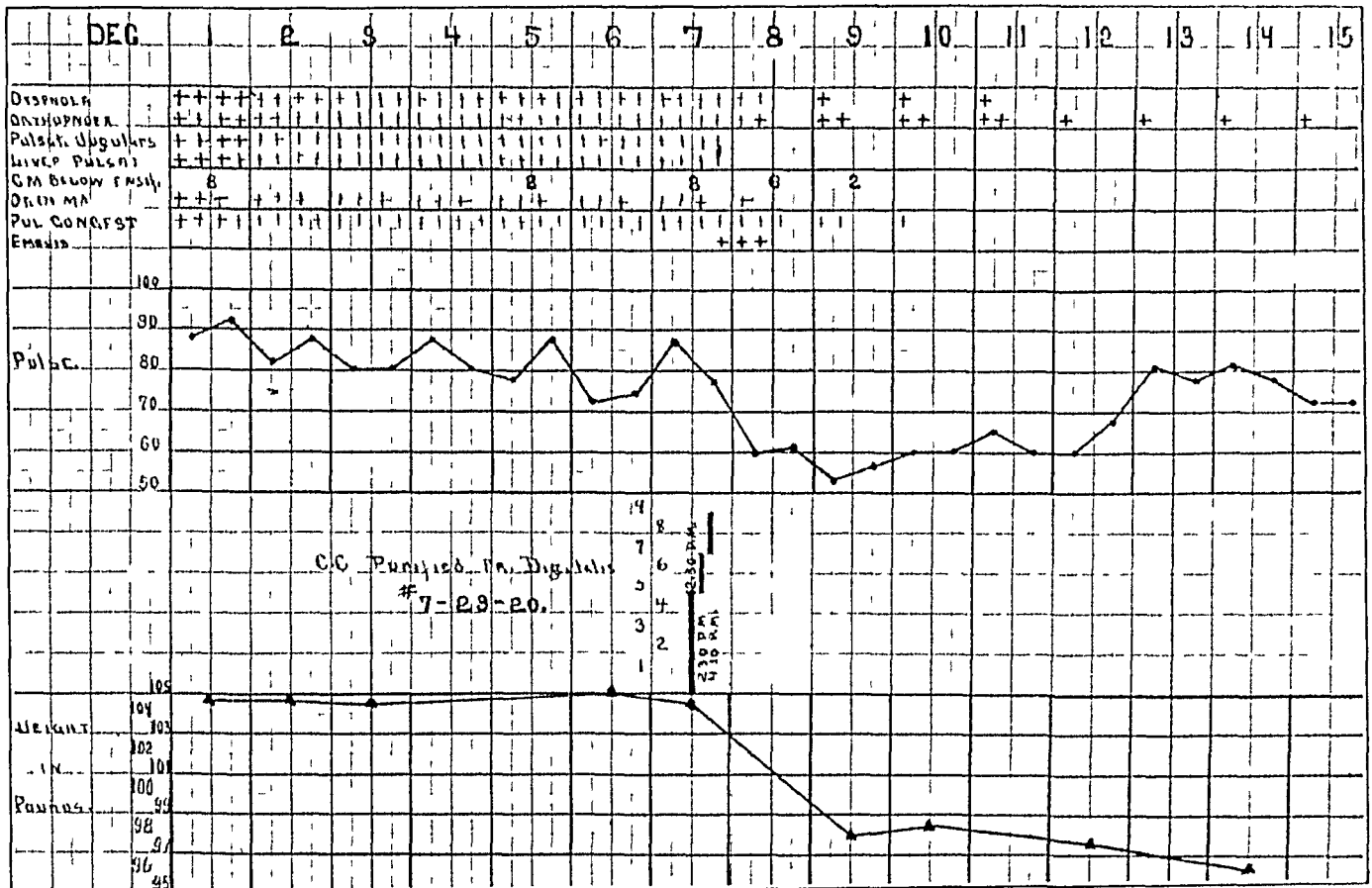


Fig 2—Chart showing course of events in patient 11, with sinus rhythm L. A., aged 30, married. Rheumatism at 12 and frequently since. First symptoms of heart failure six years ago. In hospital with heart failure in 1914 and 1920. Admitted this time Nov 27, 1920. Apical impulse visible and palpable sixth space at anterior axillary line. Double murmur at both base and apex. Diagnosis: Rheumatic heart disease with aortic insufficiency, mitral stenosis and insufficiency. Heart failure of the congestive type. Rest in bed on back rest. Salt-free diet, fluids limited to 1,000 cc. Purified tincture digitalis 7-23-20 was given Dec 7, 1920, as follows: 5 cc at 12:30 p. m., 2 cc at 2:30 p. m., and 2 cc at 4:30 p. m.

Table 3. In three of the four remaining cases preliminary control records were not obtained. The fourth patient, while presenting definite auricular fibrillation, showed no evidences of heart failure other than a slight pulse deficit. His control electrocardiogram, taken the day before

the administration of digitals, showed a lower ventricular rate than any recorded before the fourth hour after the administration. It was, therefore, impossible to assign the time of beginning effects with accuracy.

TABLE 2—SHOWING THE INITIAL AND THE FULL THERAPEUTIC EFFECTS PRODUCED, WITH THE DOSES PRODUCING THEM AND THE TIMES OF THEIR APPEARANCE, FOR PATIENTS WITH AURICULAR FIBRILLATION

No	Initial Effects	Cat Units per Lb	Time in Hours	Full Therapeutic Effects	Cat Units per Lb	Time in Hours
Purified Tincture Digitalis No 3-18-20						
26	No E K G			Slowing, removal of deficit, clinical improvement	0 144	± 24
27	Removed deficit, slowing	$\pm 0 073$	2	Clinical improvement, slowing	0 112	24
28	Slight slowing, vomiting	0 058	$2\frac{3}{4}$	Pronounced slowing, vomiting	0 084	$3\frac{3}{4}$
29	Slowing, clinical improvement, lowered T2	0 060	1	Single dose		
30	No E K G			Marked clinical improvement	0 133	35
31	Slowing, clinical improvement, reduced deficit	0 058	2	Single dose		
32	Indefinite			Slowing, pulse deficit removed	0 058	4
33	Beginning slowing	0 062	1	Clinical improvement, slowing, pulse deficit removed, diuresis	0 062	± 22
Purified Tincture Digitalis No 12-30-20						
34	Slowing, reduced pulse	0 065	1	Single dose		
35	Slowing, reduced deficit	0 053	2	Marked slowing	0 053	$-22\frac{1}{2}$
36	Slowing	0 053	1	Marked slowing, clinical improvement	0 053	$-22\frac{1}{2}$
37	Slowing	0 053	1	Slowing, reduced deficit	0 077	± 24
38	Slowing	0 063	1	Marked slowing, pulse deficit removed, clinical improvement	0 131	-48
39	Slowing	0 060	$\frac{1}{2}$	Marked slowing, clinical improvement	0 060	-21
40	Slowing	0 056	1	Slowing, clinical improvement, pulse deficit removed	0 056	± 7
41	Marked slowing, lowered T2	0 057	$-1\frac{1}{2}$	Further slowing, pulse deficit removed	0 057	$4\frac{1}{2}$
42	Marked slowing	0 057	$\frac{3}{4}$	Further slowing, clinical improvement, lowered T1	0 057	$3\frac{3}{4}$
43	Slowing	$\pm 0 056$	1	Marked slowing	$\pm 0 056$	3
Purified Tincture Digitalis No 7-23-20						
44	Slowing	0 051	1	Marked slowing, pulse deficit removed, emesis	0 090	5
45	Slowing, reduced deficit	0 073	2	Vomiting, slowing	0 073	5
Purified Tincture Digitalis No 8-19-20						
46	Marked slowing	0 048	1	Inverted T2, premature con tract	0 101	5
Tincture Digitalis No S						
47	Marked slowing	0 117	3	Supply of tincture gave out		
48	No control record			Clinical improvement, emesis, pulse deficit removed	0 149	20
Tincture Digitalis No H						
49	Slowing	0 049	5	Slowing	0 158	68
50	Slowing, premature con tract, lowered T3	0 053	5	Slowing, removal of deficit	0 090	23
51	Slight slowing	0 064	5	Slowing, block, removal of deficit, diuresis	0 330	86
52	Slowing, T2 diphasic	0 063	4	Indeterminate		

The dose producing definite initial effects varied from 0 04 to 0 073 cat unit per pound with an average of 0 056 cat unit for all cases. If the cases with sinus rhythm be considered alone, the average dose producing definite initial effects is 0 054 cat unit, as compared with an average of 0 058 cat unit for the cases with auricular fibrillation. The

maximum variations from the average are 28 per cent below and 30 per cent above, with only six cases varying by as much as 15 per cent

Thirteen patients in whom definite initial effects were recorded after the administration of one or the other of the two galenical tinctures showed an average dose of 0.087 cat unit per pound for the production of those effects. In these the range of variation extended from 39 per cent below to 40 per cent above the average dose.

TABLE 3—SHOWING AVERAGE DOSES OF PURIFIED AND OFFICIAL TINCTURES IN FRACTIONS OF CAT UNIT PER POUND OF BODY WEIGHT

	First Effects	Time in Hours	Full Effects	Time in Hours	Number of Cases
Purified Tinctures					
Auricular fibrillation	0.058	1.26	0.081	15.7	18
Sinus rhythm	0.054	1.20	0.084	10.3	15
All cases	0.056	1.23	0.082	13.4	33
Official Tinctures					
Auricular fibrillation	0.069	4.4	0.212	43	5
Sinus rhythm	0.096	3.75	0.213	44	9
All cases	0.087	3.98	0.213	43.7	14

These variations in dose from the average indicate a somewhat greater variability in the absorption of the galenical tinctures than in that of the purified preparations, but they are misleading in that they fail to bring out the true magnitude in the variability in the absorption of different tinctures. This is more clearly shown in Table 4.

It has previously been shown that the size of the dose of digitalis is not materially influenced by the presence or absence of auricular fibrillation,¹ and this fact is here confirmed. In Table 4, therefore, the average doses producing initial effects are inclusive of all cases. The average has been determined for each preparation separately, and the variations are shown for each in terms of percentages of the average dose for that preparation. To this we have appended the corresponding figures reported in a previous paper¹ and based on the administration of seven different official tinctures to twenty-one patients.

From Table 4 it is seen that the greatest total range of variation among the purified tinctures amounts to 44 per cent of the average dose—23 per cent below and 21 per cent above. For the official tinctures included in the present study the maximal range of variation in dose is 77 per cent—25.7 per cent below and 51.5 per cent above—or not far from twice as great a variation as in the case of the purified specimens. If we compare the range of variation of the purified tinctures with that observed among seven different official tinctures previously studied the contrast is even greater, namely a total range of 44 per cent for the former as against 116 per cent for the latter.

The relatively greater uniformity of the absorption of the purified preparations than of the official tinctures is also shown by a comparison

of the average doses of the several preparations of a given class. As those doses are expressed in terms of activity of the drug in all cases their comparison clearly reflects differences in absorbability as shown by the appearance of evidences of action of the drug on the heart. The average doses of the purified tinctures shown in Table 4 differ from one another by only 0.014 cat unit, while those of tincture S and tincture H differ by 0.049 cat unit per pound. It is interesting to note also that while tincture S was less readily absorbed, as shown by the larger dose required, its absorption was apparently decidedly more uniform than was that of tincture H. The criteria for the determination of the development of full therapeutic effects from the administration of digitalis are, of necessity, less precise than are those marking the onset of the first demonstrable action. For this reason a study of the average doses producing full therapeutic effects and the variations from the

TABLE 4—SHOWING AVERAGE DOSES PRODUCING INITIAL EFFECTS WITH RANGE OF VARIATION

Preparation	Average Initial Dose Cat Unit \times Lb	Range of Variation in Percentage of Average	
		Below	Above
3-18-20	0.062 (12)*	9.6	17.7
12-30-20	0.057 (12)	10.5	14.0
7-23-20	0.052 (6)	23.0	21.0
8-19-20	0.048 (3)		
Tincture S	0.115 (6)	13.0	6.0
Tincture H	0.066 (8)	25.7	51.5
Seven tinctures†	0.095 (21)	59.0	57.0

* Number of cases

† Taken from "Digitalis Dosage," loc cit

averages are less satisfactory in indicating differences in absorbability of the two types of preparation. Furthermore, in approaching the induction of full therapeutic effects, or minor toxic action, it was our custom to reduce the size of the individual dose which was given at six hour intervals so that the time over which administration was extended varied widely and sometimes was sufficient to permit of an appreciable elimination of the drug. This was specially true in the cases of the official tinctures, which were absorbed so much more slowly that it sometimes required more than three days for full digitalization.

Nevertheless, reference to Table 3 shows that an average of nearly two and one half times as much of the galenic tinctures as of the purified was required for the production of full therapeutic effects. Since throughout the doses are expressed in terms of the same biologic unit of activity, this difference in dose must be due to differences in absorption, the purified tinctures being absorbed much more completely than the galenical. This is also shown to be the case if we compare the average dose here established for the purified tincture—0.082 cat unit

per pound—with that of 0.146 cat unit per pound previously established for seven different official tinctures of widely divergent activity. The average total full therapeutic dose of the two tinctures employed in the present series of observations is materially higher than that previously established due to the fact that the two tinctures here studied were therapeutically unsatisfactory owing to poor absorption. Tincture S is the preparation used by Dr. B. S. Oppenheimer⁹ in three patients who took amounts equivalent to 134 c c, 193 c c and 233 c c, respectively, in twenty-three, thirty-eight and forty-three days without significant digitalis action. If these totals were divided into uniform daily doses they would have amounted to from 5 to 5.8 c c per day, or about twice the average daily dose of a well absorbed tincture of average activity which can be taken continuously without the development of cumulation.

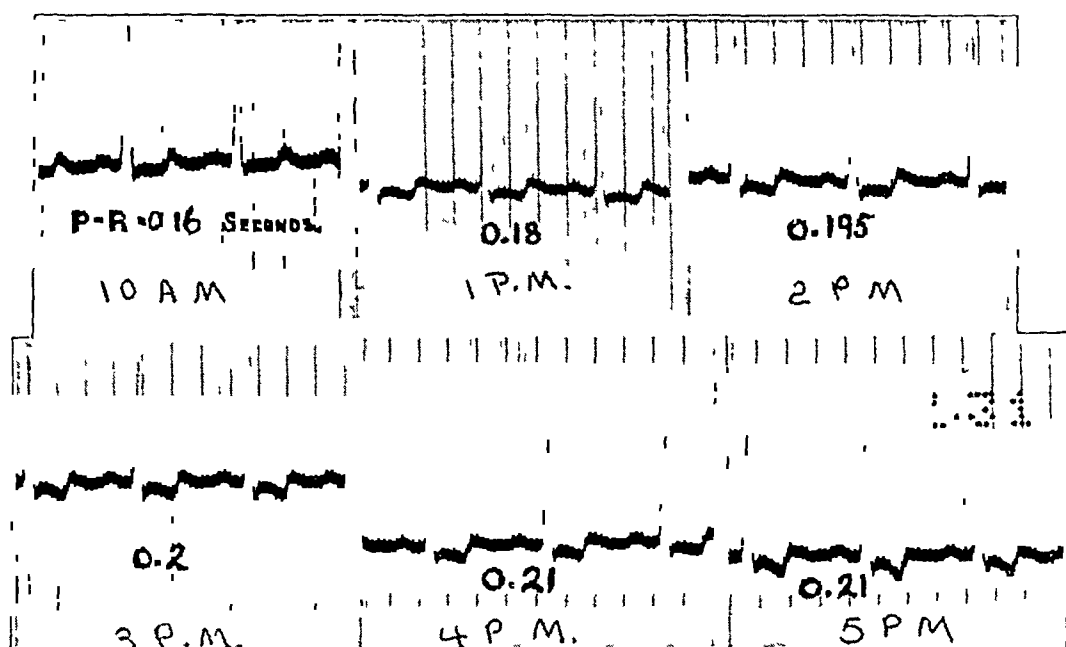


Fig. 3—Chart showing control electrocardiogram—10 a m, and hourly records beginning one hour after single dose of purified tincture of digitalis amounting to 0.045 cat unit per pound. Patient 13. The figures give the average length of the P-R intervals taken from several consecutive beats. The decrease in the height of the T wave and its final inversion are also shown.

SUMMARY Purified tincture of digitalis is shown to be absorbed from the human alimentary canal both more nearly uniformly and more completely than are different official tinctures, as measured by the ranges of variation of the doses causing initial effects from the average doses for their production, and by the difference in the amounts required for the production of full therapeutic effects.

Rate of Absorption—Tables 1 and 2 show the time in hours from the administration of the first dose to the appearance of the first

demonstrable evidences of absorption and to the development of full therapeutic effects. From these data the average times shown in Table 3 have been calculated. It is seen that the average time from administration to onset of evidences of absorption is just under one and a quarter hours in the case of the purified tinctures, while it is just under four hours with the galenic tinctures, or three times as fast with the former as with the latter. The difference is probably even greater than here shown, for we had not anticipated the onset of evidences of absorption in less than one hour so that in the majority of our cases the first cardiogram was not taken until one hour after the initial dose, and in some not until two hours or more after the dose.

Of the thirty-three patients receiving the purified tinctures, twenty-five showed definite evidences of absorption of the drug in one hour or less, and among the remaining eight the first electrocardiogram was taken one hour after the initial dose in only four, in one of whom the control record, however, was taken three days before and showed a slower heart rate than any recorded for three hours after the digitalis was given. In this patient hourly records of the pulse deficit were taken and this had fallen markedly in two hours. In three of the remaining four cases there was no electrocardiographic control record, the hourly pulse deficit record again being used as the guide to digitalis action. In the eighth patient the first electrocardiogram was not taken until two and three quarter hours after the administration of the digitalis. In one of the patients receiving the purified tincture absorption was evident in half an hour and in a second in three quarters of an hour.

The average time required for the absorption of the official tinctures is three times as long as for the purified tincture, and the individual patients show a much wider range of variation. Thus only one out of the total of fourteen patients showed definite evidences of absorption in as little as one hour, and one other in two hours, while five required five hours and one required seven hours to absorb sufficient tincture to produce definite evidences of the action of the drug.

When we consider the average times required to produce full therapeutic effects, a similar relationship is manifested between the rates of absorption of the two types of preparation, the purified tinctures producing full therapeutic effects in less than one-third of the time required for the galenic tinctures. Among the total of thirty-three patients showing full therapeutic effects from the purified tinctures only seven required twenty-four hours or longer for the development of these effects. Of these seven, one (No. 6) received no further digitalis until thirty-six hours after his initial dose, and in the case of another (No. 38) the interval between the initial dose and continuation of administration was thirty hours. In the remaining five no such intervals elapsed, and the explanation for the delayed absorption must be sought

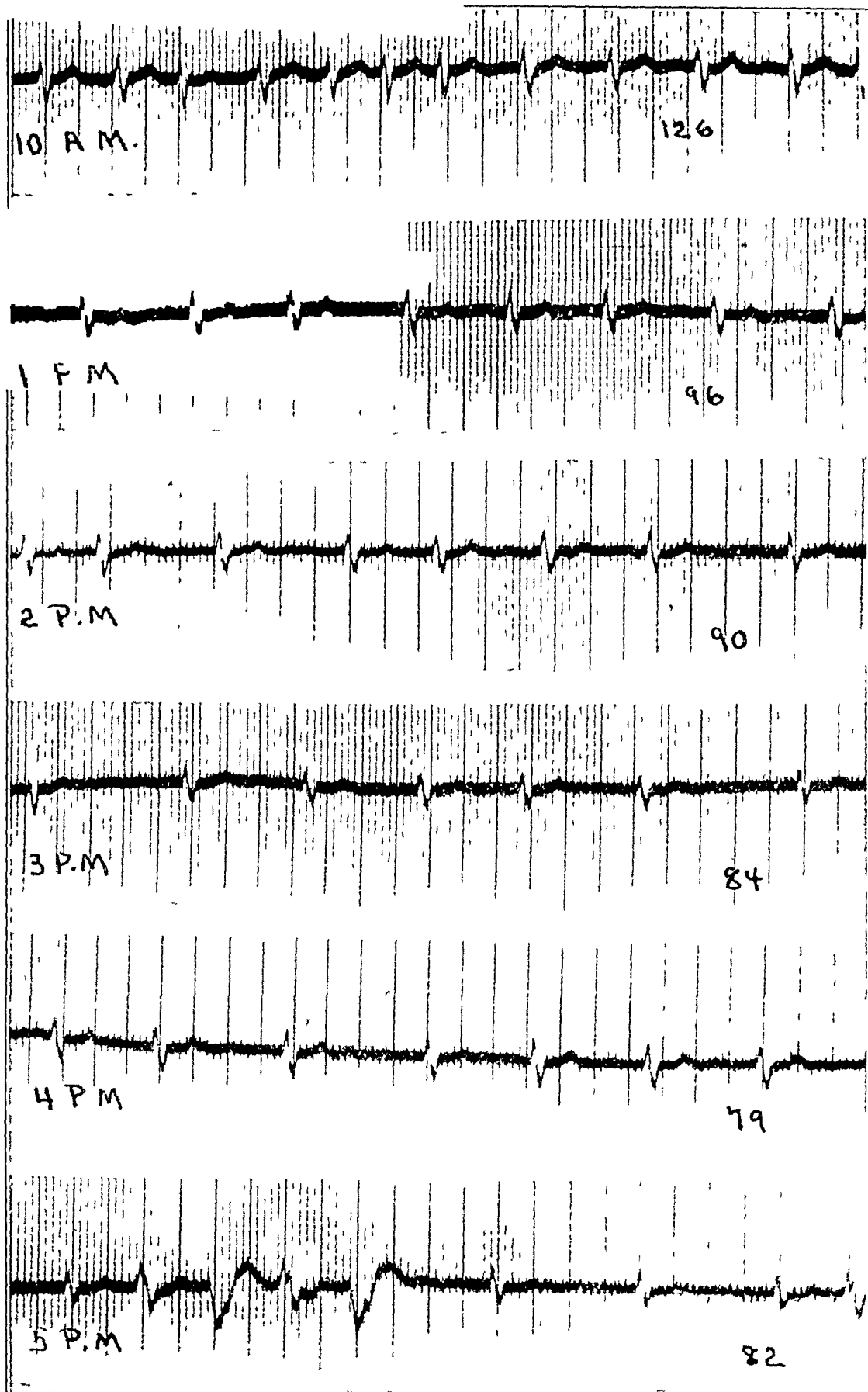


Fig 4—Chart showing control electrocardiogram—10 a m , and hourly records beginning one hour after single dose of purified tincture of digitalis amounting to 0056 cat unit per pound Patient 40 The figures to the right indicate the ventricular rates obtained from counts of all three leads Lead II* only is reproduced here

in the patients themselves in three of the cases (Nos 1, 27 and 30) It seems probable that these were patients who, for some reason as yet unknown, were unable to absorb the drug with the usual rapidity In the cases of the other two (Nos 26 and 37) the full effects were first observed after the lapse of the night, and the precise time of their appearance was not determined The times in these two are marked with a plus-minus (\pm) sign to indicate the uncertainty of the interval

Further, among the purified tincture group nineteen showed fully developed therapeutic actions of the drug in five hours or less, two showing them within three hours following the administration of a single dose These two patients, however, were unusually susceptible to the action of the drug, responding to as little as 68 per cent of the average total dose required

Contrasting with these figures are those for the individual cases of the galenic tincture group, among which only one patient developed full therapeutic effects in less than eighteen hours, that one responding in seven hours The average time for the development of full therapeutic effects in this group is materially longer than that previously recorded¹ for twelve cases receiving different samples of galenical tincture in large doses, namely, twenty-eight hours This is due to the fact that the two tinctures employed in the present investigation were less readily absorbable than were those used in the previous study, as has been mentioned earlier in the discussion of the dosage

Summary Purified tinctures of digitalis are shown to be absorbed from the human digestive tract in sufficient amount to produce definite cardiac actions in an average of less than one hour and a quarter, and in amounts sufficient to produce full therapeutic effects in an average of a little more than thirteen hours Their absorption is more than from two to three times as rapid as is that of different galenic tinctures, whether judged by the development of initial or of full therapeutic effects

Nausea and Vomiting—Digitalis has been shown¹¹ to produce nausea and vomiting in animals after the extirpation of the gastrointestinal tract, and the action was assumed to be direct on the vomiting center since no other method was known It was also shown¹² that the same mechanism was responsible for the nausea and vomiting observed in man after the administration of digitalis Hatcher and Weiss¹³ have pursued the problem further and have very recently shown that the vomiting produced by digitalis and its allies in animals is the

11 Hatcher, R A, and Eggleston, Cary The Emetic Action of the Digitalis Bodies, *J Pharmacol & Exper Therap* 4 113, 1912

12 Eggleston, Cary Clinical Observations on the Emetic Action of Digitalis, *J A M A* 61 757 (Sept 6) 1913

13 Hatcher R A, and Weiss, Soma Seat of the Emetic Action of the Digitalis Bodies To be published

result of protective reflexes arising in the heart when it is poisoned by the drug. These cardiac reflexes apparently pass to the medullary vomiting center through afferent sympathetic fibers mainly, and to a lesser extent through afferent fibers contained in the vagi.

Following the work of Hatcher and Weiss we have reexamined the results of the study of digitalis emesis in man and we are now able to present evidence that digitalis causes vomiting in man by this same cardiac reflex mechanism. The clinical evidence shows (1) that digitalis does not cause emesis in man by local irritant action in the digestive tract, (2) that its emetic action in man results only after the absorption of a sufficient quantity of the drug, (3) that definite evidences of action of digitalis on the human heart are almost invariably to be found before the appearance of either nausea or emesis. Thus it was stated,¹² "of 106 courses of digitalis treatment in cardiac disease resulting in the appearance of nausea or vomiting, 100, or 94.3 per cent, showed indisputable evidence [by action on the heart] of absorption of the drug prior to the onset of these symptoms. In fifty-five observations on cases with auricular fibrillation, nausea or vomiting was associated with [cardiac evidences of] the absorption of the drug in every instance."

Nausea or vomiting developed in twenty patients in the present series at some time during the administration of digitalis, and these have been brought together in Table 5. In this table are shown the cardiac phenomena induced by the digitalis before the appearance of either nausea or emesis, together with the doses causing the earliest demonstrable evidences of absorption, those causing nausea or emesis, and the times elapsing between the first dose and the development of earliest effects and of nausea or emesis. Reference to this table shows that in eighteen of the twenty patients nausea or emesis developed only after amounts of the drug had been given which were considerably greater than those required for the production of beginning action on the heart. In the entire series of patients the emetic dose ranged from one the same size as that producing the initial effects in the average case to a dose four and one third times as large as the average, in the case of the purified tinctures. The average emetic dose of the purified tinctures was 0.113 cat unit per pound, or almost twice that required to produce initial evidences of action on the heart. Similar relationships are found among the cases receiving the galenic tinctures. Nausea or emesis developed after the administration of a single dose of the purified tincture in two patients. One of these showed definite evidences of the development of the action of the drug on the heart three hours before the appearance of emesis. The other patient vomited after taking digitalis at a time before any electrocardiograms had been taken these records having been unduly delayed. In every case but this definite evidences of cardiac action preceded the appearance of the vomiting.

The evidence supplied by these cases shows that in every instance in which observations were made early enough digitalis induces emesis in man only after the development of a more or less pronounced action on the heart. This is in perfect agreement with the observations of Hatcher and Weiss, which show that the nausea and emesis produced by digitalis arise reflexly from the drug's action on the heart. In view of these facts and the extremely close parallelism between all of the other actions of digitalis in the lower animals and in man the conclusion is justified that in the human being also nausea and vomiting are produced by digitalis as the direct result of an intoxication of the heart sufficient to provoke the protective mechanism of reflex stimulation of the vomiting center, the stimulus arising within the heart. The development of nausea or vomiting in the course of the therapeutic administration of digitalis must henceforth be regarded as among the surest and most valuable evidences of intoxication of the heart, and demands the immediate cessation of further administration, at least temporarily.

Dosage of Purified Tincture—The figures presented in Table 3 indicate that the average initial dose of the purified tincture required to produce the earliest demonstrable effects on the heart is 0.056 of a cat unit per pound of the patient's body weight. While this figure represents approximately the average dose which will produce these effects with certainty, it is not the average minimum effective dose, since in many patients the initial dose given was materially larger than the smallest which produced similar effects in other patients. Thus definite cardiac actions followed doses smaller than the average in thirteen of the patients, the dose in four being 15 per cent or more below the average. The average dose of the purified tincture used to produce initial effects is 30 per cent larger than that established for commercial crystalline digitoxin, and two thirds that established for a variety of official tinctures.

Full therapeutic effects followed an average total dose of the purified tinctures amounting to 0.082 of a cat unit per pound, or an amount 44 per cent greater than that used to produce the initial actions. In ten of the patients full therapeutic effects resulted from doses approximately the same as the average employed for the induction of initial effects. Seven of these ten patients showed fibrillation of the auricles and when the pulse deficit had been removed and the ventricular rate had been slowed to about 70 beats per minute we deemed that full therapeutic digitalization had been accomplished and temporarily discontinued the administration of the drug. The remaining three patients had sinus rhythm and two of them showed a change from an upright T wave to a diphasic one, with marked prolongation of the conduction time and pronounced slowing of the whole heart. Simultaneously there was marked improvement in the clinical signs of heart failure. The drug was pushed further in one of these (No. 5) with the development

of premature contractions. The tenth patient, the third of those with sinus rhythm, showed such marked clinical improvement that the drug was stopped. We will show subsequently, however, that much larger total doses than these, or than the average full therapeutic dose, can be taken by most patients without danger.

TABLE 5—SHOWING CARDIAC ACTION OF DIGITALIS APPEARING BEFORE EMESIS, DOSES CAUSING FIRST EFFECTS AND DOSES CAUSING EMESIS

Number	First Effects		Cardiac Phenomena Before Nausea or Vomiting	Nausea or Emesis	
	Dose in Cat Units	Time in Hours		Dose in Cat Units	Time in Hours
Purified Tinctures					
1	0.066	1	Lowered T, increased P-R	0.150	42
2	0.067	2	Lowered T, increased P-R, V P C *	0.088	4.66
5	0.059	1	Lowered T, increased P R	0.113	42
6	0.061	1	Lowered T	0.190	72
11	0.051	1	Inverted T, increased P R	0.092	6
12	0.040	2	Increased T, increased P R	0.073	5
13	0.045	1	Lowered T, increased P R	0.090	5†
16	0.050	1	Lowered T	0.082	4†
28	0.058	2.75	Increased premature contract	0.058	1.75§
32	0.062	1	Heart block, V P C	0.131	90‡
38	0.063	1	Heart-block	0.250	81‡
44	0.051	1	Heart block	0.090	5‡
45	0.073	2	Heart block, increased V P C	0.073	5‡#
46	0.048	1	Lowered T, heart block, V P C	0.101	12
Official Tinctures					
19	0.117	2.33	Lowered T, V P C	0.173	18
20	0.121	1	Lowered T	0.390	84
22	0.060	2	Lowered T, increased P-R	0.114	49
23	0.057	3	Lowered T, increased P-R	0.260	74
24	0.078	3	Lowered T V P C	0.260	42
48			Heart block	0.119	20‡

* V P C indicates ventricular premature contractions

† T in Lead II inverted just before nausea developed

‡ Shortly after emesis records showed auricular fibrillation, runs of ventricular paroxysmal tachycardia, etc. Good recovery

§ First electrocardiogram taken 2.75 hours after dose. Single dose only in this patient

¶ The heart block here is that commonly observed after digitalis in auricular fibrillation, in all cases so marked were fibrillating

Only a single dose given to this patient

The average therapeutic dose of the purified tinctures is only 20 per cent greater than that of crystalline digitoxin and is but 55 per cent of the corresponding dose of the average well absorbed tincture of digitalis. It is evident that this simple purification of digitalis yields a substance which approaches the very costly crystalline digitoxin in biologic activity.

Two discrepancies between the averages given in the present report and those stated in previous papers demand explanation. The average full therapeutic dose of the purified tincture of digitalis was given as 0.159 cat unit per pound of body weight in the preliminary paper on the subject, or almost twice that shown in the present series of cases. The discrepancy is due to two factors:

1. The former dose is too large because we were then experimenting with a substance new to us and for the sake of caution administered it much more slowly and in much smaller individual doses, thus taking two or three times as long for complete digitalization as the average required in the series here discussed.

2 The present total dose is probably somewhat too low for a true average, because we used relatively very large initial doses in most patients, and because we often discontinued further administration when a moderate degree of clinical improvement had been induced, rather than continue to the point of producing evidences of minor intoxication. We believe that 0.1 cat unit per pound more nearly represents the average full therapeutic dose as the drug would be given in a large series of cases where many patients would not require very rapid digitalization, and for our continued use of the drug in a routine hospital service we are employing this figure with satisfactory results as a basis of our calculations. This would give a maximal initial dose of 0.05 cat unit per pound, which, as Tables 1 and 2 show, did not in a single instance produce even minor intoxication.

The second discrepancy is that between the average full therapeutic doses of the two galenic tinctures used in the present series of cases and that formerly established. The present dose of 0.213 cat unit is 1.44 times as large as the average previously stated. This is due to the fact that the two tinctures used here were poorly absorbed, and it was anticipated in selecting them for use that considerably larger amounts would be required than in the case of the average well absorbed tincture of good activity. As it is the difference is less than we had expected to find.

The Body Weight as a Basis for Calculation of Dose—We have already referred to several papers in which the validity of the body weight method of estimating the dose of digitalis has been confirmed and established, but Wedd⁷ says that no constant relation could be established between the body weight and the amount of digitalis which could be given in his cases. He does not give the details in his series of cases, so that it is not possible to subject his observations to a critical analysis. He states, however, that the average total dose required for the production of toxic symptoms was 52 c c in the case of his second tincture which had an activity of 85 milligrams per cat unit, the toxic dose having varied from 20 to 100 c c. It is quite evident from his figures that this sample of digitalis, as well as his first one, was one in which the absorption was very irregular and usually very poor, since the average tincture of equal activity which is well absorbed will usually produce toxic symptoms after a total dose of about 25 c c, and often after somewhat less. Further, Wedd gave daily doses which required from two to eight or more days for the development of full digitalization. With the larger total doses, therefore, the more or less variable factor of the elimination of the drug must have assumed an important role especially since there is a considerable range in the rate of elimination of digitalis in different patients.

It has never been contended that the average doses established on the basis of body weight were precise. In fact, in the original paper dealing with the subject it was specially emphasized that there was a considerable range of variation in individual cases from the average. The average dose was offered as a basis for the *approximate* estimation of the total amount of digitalis which would be required for the production of therapeutic digitalization. As such it has proved to be essentially correct in spite of the individual cases not infrequently encountered in which the actual amount required differs more or less widely from the average. The method has been used by one of us as a routine in estimating the dose for over five years, with satisfactory results in several hundred cases, the great majority of which have responded satisfactorily to a dose closely approximating the average. It is confidently believed, therefore, that Wedd's failure to observe any constant relationship between the size of the dose and the body weight of his patients is due to the two factors mentioned.

Variation in the Patient's Absorptive Capacity—A second factor in the question of absorption which merits brief discussion, but which cannot yet be entered upon in detail for want of sufficient data, is the question of the variations in the capacity of different patients to absorb digitalis. It is well known that different normal animals of the same species vary considerably in their capacity to absorb a given drug from the digestive tract. It is certain that a similar variation in this capacity exists in normal man, and it is probable that in the presence of a disturbed circulation this variation is enhanced. Data obtained in the present series of cases confirm this contention.

If we refer to Tables 1 and 2 and consider the full therapeutic doses taken by the thirteen patients who received purified tincture 3-18-20 we see that the largest dose required to produce full therapeutic effects within twenty-four hours was two and one half times as great as the smallest which sufficed to produce analogous effects, and one and one half times the average dose required with this specimen. Administration having been completed within twenty-four hours in all but three of these patients, and within forty-eight hours in the remainder, elimination did not play an important part in determining the total amount required. Only two explanations remain to account for this variation in dose. Either variation in the susceptibility of the heart to the action of digitalis or variation on the part of the patients in their capacity to absorb the drug.

Our experience leads us to believe that both these factors are concerned to varying degrees. Thus in patients with heart failure due to auricular fibrillation and showing a high grade of pulse deficit we are convinced that complete recovery from the attack of failure not infrequently follows the beginning restoration of the circulation by a

relatively small dose of digitalis. The small amount of digitalis is just enough to slow the ventricular rate to a moderate degree and the ensuing improvement in the circulation breaks a vicious circle primarily through a progressive improvement in the nutrition of the heart initiated by greater diastolic rest and improved coronary circulation. In other cases of the same type this does not occur and it is necessary to push vigorously the administration of digitalis. Among this latter group cases are observed in which relatively very large doses are required and in such we believe the individual capacity for absorption may often be relatively poor.

The best illustrations of probable defective capacity to absorb digitalis are seen, however, among patients with sinus rhythm. In these there is much less likelihood of the breaking of a vicious circle by a small dose, since the essential element in the causation of failure is not the same. Among these we find far fewer instances of full therapeutic response to a dose much below the average. The tendency to exceed the average markedly is also somewhat less frequent. We, therefore, believe that the wide variations in dose sometimes encountered with a given sample of digitalis are probably referable to variations in the capacity of the individual patient to absorb the drug although there is always the possible factor of a relative insusceptibility of the heart itself to the action of the drug. Furthermore, it has been our general experience that when a patient is found to absorb one specimen of digitalis promptly, he almost invariably absorbs other good specimens equally well, though not necessarily to precisely the same extent, or with quite the same promptness. Finally, we continued the administration of each of the samples of both purified and galenic tinctures beyond the development of full therapeutic effects in one or more patients for the purpose of testing the matter of insusceptibility of the heart. From the twenty-three instances in which this was done we select a few for illustration.

Patient 38 showed a marked degree of ventricular slowing only after 0.131 cat unit per pound of body weight, with removal of his pulse deficit and a satisfactory therapeutic response, but it was necessary to increase the total dose taken to 0.250 cat unit, or nearly double, before the only toxic symptom—nausea—developed. In patient 34 a single dose of 0.065 cat unit per pound produced ventricular slowing and reduced the pulse deficit in one hour. After an interval of 56 hours the same preparation was continued at the rate of 0.069 cat unit per pound daily until a total of 0.237 cat unit per pound had been taken without the development of any toxic symptoms. Analogous variations are seen in several other cases. We are convinced that the probable explanation for the poor absorption in these cases, especially in those involving the purified tinctures, is referable to the patient's individual

deficiency in the capacity to absorb digitalis. We also believe that the differences in the capacity to absorb digitalis, and not cardiac insusceptibility, largely account for the variations in dosage observed in a series of patients receiving a single sample of the drug.

SUMMARY

1 The absorption of high grade specimens of tincture of digitalis from the digestive tract of man is almost invariably sufficiently uniform to permit the establishment of a satisfactory working average total dose in terms of the cat unit of activity per pound of the patient's body weight.

2 Specimens of tincture of average biologic activity are occasionally encountered which are therapeutically unsatisfactory on account of poor absorption from the alimentary canal.

3 Tincture of digitalis shows definite evidences of action on the heart in from two to four hours after oral administration to man.

4 Poorly absorbed tinctures may require more than five hours for the development of demonstrable cardiac action.

5 A method of preparing and standardizing a purified tincture of digitalis is described.

6 The purified tincture is shown to be absorbed from the human digestive tract more rapidly and more nearly uniformly than are different specimens of official tincture of average biologic activity.

7 Considerable variation in the capacity of different individuals to absorb digitalis is shown to exist.

8 Evidence is offered to show that digitalis causes nausea or vomiting in man by reflexes arising in the heart as a result of its intoxication.

9 An average total dose of the purified tincture for oral administration to man is established on the basis of its cat unit of activity and the patient's body weight.

CONCLUSION

While the purified tincture of digitalis is more nearly uniformly absorbed by man than are official tinctures obtained from different sources, it is, perhaps, not more uniformly absorbed than is any single tincture of good quality. It is probable that crystalline digitoxin is slightly more uniformly absorbed than the purified tincture, but the former does not seem to be of uniform activity. Each specimen of crystalline digitoxin, therefore, would appear to require biologic assay before it could be used safely in effective doses, unless one wishes to proceed very cautiously with its administration, in which case there would be delay in obtaining its full therapeutic effect.

DELAYED CONDUCTION THROUGH THE RIGHT AND LEFT BRANCHES OF THE ATRIOVENTRICULAR BUNDLE *

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INTRODUCTION

The question of the diagnosis of branch lesions in clinical electrocardiography is still largely unanswered. There are at least two important reasons for this. In the first place, although an abundance of experimental data pertaining to complete bundle branch block in animals has been accumulated, the extent to which the results can be applied to man is very uncertain. A further difficulty is discovered in the recent papers of Fahr,¹ who would completely reverse the previous conceptions of branch lesions and preponderating ventricular hypertrophy.

In the second place, our knowledge of the anatomy of the atrioventricular bundle and the Purkinje system is far from complete. We have not been sufficiently critical of researches on their normal structure, more especially in relation to the methods adopted. We have fallen into the habit of easily visualizing the nodes and tracts of the atrioventricular conduction system in the human heart, overlooking the fact that the technic which has generally been employed in examining these structures has failed entirely to bring to light the finer details of the Purkinje system. Is it not significant of the inadequacy of the ordinary technic that it has never until recently² succeeded in demonstrating Purkinje fibers in the wall of the auricle? The pathologist's failure to find in the conduction system the organic lesion so confidently predicted from the electrocardiogram is a matter of frequent record. That many of these conduction defects are functional and transient, we know, but on the other hand, more such defects than we suspect are due to actual lesion. Instead of revising our interpretation of tracings, let us inquire into our pathologic methods, and see what need of revision may be there. I think we shall find that the method of clinical electrocardiography is so much more sensitive and exact than our present pathologic methods that we need not cast aside all

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1 Fahr Arch Int Med **25** 146 (Jan) 1920 *ibid*, **27** 126 (Jan) 1921.

2 Holmes J Anat **55** 269, 1921. Holmes found Purkinje fibers in the auricle in two animals. He believes (erroneously) that he was the first to make this discovery.

our clinical conceptions from want of postmortem confirmation. In the light of these considerations, it is probable that past attempts to correlate clinical with pathologic findings have served more to obscure than to elucidate the problem. The truth of this observation is very clear to anyone who has encountered in his own experience, and in the literature, its many examples. Contradiction and confusion are everywhere apparent.

It is my belief that we shall be forced to discard many of the conclusions based on earlier methods of anatomic study, and take a fresh start. I wish to draw the attention of all students of this problem to the monograph of Van der Stricht and Todd³ as offering an adequate basis on which more exact observations may be made in the future. These investigators have contributed much to our knowledge of the anatomy, normal and abnormal, of the Purkinje system. They were the first to succeed in demonstrating fibers of Purkinje in the auricular walls. The importance of the endeavor to correlate clinical electrocardiograms with pathologic findings such as these, as Carter⁴ has done, cannot be overemphasized, but it is much too early for sweeping generalizations. It is of interest here to mention the researches of Oppenheimer and Rothschild⁵ in "arborization block." Their results have been vigorously attacked from various standpoints, notably by Wilson and Herrmann,⁶ Smith⁷ and Drury⁸. This criticism loses some of its force in the presence of better understanding of the anatomy and pathology of the conduction system.

INCOMPLETE BUNDLE BRANCH BLOCK

The effect on the electrocardiogram of delay in conduction through the right and left branches of the atrioventricular bundle was first suggested by Lewis⁹ in 1912. He observed the phenomenon in the course of an experiment, and strongly suspects that it occurs in certain patients. Wilson and Herrmann¹⁰ elaborated this idea in the endeavor to explain certain aberrant electrocardiograms which are not at all characteristic of complete branch lesions as at present understood, yet display conspicuous increase in the QRS interval. They proposed to show that the principal effect of a lesion which delays, but does not completely interrupt, the passage of the impulse through one of the main branches of the atrioventricular bundle will be a change in

3 Van der Stricht and Todd. Johns Hopkins Hosp. Rep. **19** Fasc. 1, 1919.

4 Carter. Arch. Int. Med. **22** 331 (March) 1918.

5 Oppenheimer and Rothschild. J. A. M. A. **69** 429 (Aug. 11) 1917.

6 Wilson and Herrmann. Arch. Int. Med. **26** 153 (Aug.) 1920.

7 Smith. Arch. Int. Med. **26** 205 (Aug.) 1920.

8 Drury. Heart **8** 23, 1921.

9 Lewis. Heart **3** 279, 1912.

10 Wilson and Herrmann. Heart **8** 229, 1921.

the time relation of the right and left ventricular effects, and, therefore, an abnormal combination of the dextrocardiogram and levocardiogram. They endeavored to demonstrate this both graphically and experimentally. Using Lewis' measurements and his method of algebraic addition of the dextrocardiogram and levocardiogram, they determined the effect on the resultant curve of adding the dextrocardiogram and levocardiogram in varying time relations. They found that this procedure produces curves which are transitional in form and Q R S interval between the normal complex and the complex of branch lesions. The calculated bicardiogram gradually takes on the form of the levocardiogram or dextrocardiogram, depending on which is made to precede the other. A time difference of 0.005 second produces a very conspicuous change, and a discrepancy of 0.015 second completely alters the character of the bicardiogram.

The experimental procedures employed in the hope of producing transitional complexes were (1) Vagus stimulation in the presence of right bundle branch block (2) Bilateral bundle branch block (3) Stimulation of the right ventricle in right bundle branch block. All succeeded to a certain extent in producing transitional complexes, especially the last. A typical curve shows at one end a fully developed dextrocardiogram, at the other a fully developed levocardiogram, and many interposed combination complexes whose contour and Q R S interval depend respectively, on which of the two components precedes, and by how great a period of time. If the right and left ventricular effects occur in normal time relation, the result is a complex which very closely approximates the physiologic curve as shown in the control. If one of the components is of greater amplitude than the other this will affect the amplitude of the combination complexes proportionately. Furthermore, in the experiments in which the extrasystolic dextrocardiogram was combined with the supraventricular levocardiogram it could be determined exactly by how great an interval the one preceded the other, inasmuch as each followed a recorded event by a definite interval.

The conclusions reached by Wilson and Herrmann from their experiments are

- 1 Combination complexes in which the dextrocardiogram precedes the levocardiogram by a considerable interval are transitional in outline between the normal complex and the complex of left bundle branch block.

- 2 Combination complexes in which the levocardiogram precedes the dextrocardiogram by a considerable interval are transitional in outline between the normal complex and the complex of right bundle branch block.

- 3 Combination complexes in which the levocardiogram and dextrocardiogram begin at almost the same instant resemble the normal type of complex closely.

- 4 All combination complexes except those of the third class are diphasic and have a Q R S interval intermediate between the natural Q R S interval and the Q R S interval of bundle branch block.

5 The T wave of complexes formed by asynchronous combination of dextrocardiogram and levocardiogram is transitional in outline between the normal T wave and that of the fully developed bundle branch block complex.

The experiments of Wilson and Herrmann are noteworthy because they throw light on a little understood aspect of the problem of deficient branch conduction. Our case is considered worthy of report because the electrocardiograms reproduced nearly all of the phenomena obtained by Wilson and Herrmann from their experimental animals.

REPORT OF CASE

The patient, a man, aged 60, was admitted to the hospital for the first time Oct. 14, 1920.

Present Illness—Patient has been incapacitated for three years on account of shortness of breath and weakness. He has apparently been in a state of relative cardiac decompensation throughout this entire time. He has suffered frequently from palpitation, and has had dependent edema except when at rest in bed. In recent years it has been necessary for him to get up frequently at night to pass his urine, sometimes as often as every five minutes.

Past History—The only point of importance is the definite history of repeated attacks of articular rheumatism. These attacks have no doubt sustained a definite relation to part, at least, of the patient's present cardiac disability.

Physical Examination—Patient is sitting up in bed, very uncomfortable on account of shortness of breath. He complains of no pain. There is slight edema of the ankles.

Lungs The physical signs of the lungs are those of increase in volume and diminution in extensibility, together with increase in density at the right base from accumulation of fluid in the pleural cavity.

Heart The median portions of both costal margins move toward the median line during inspiration, and the lower end of the sternum moves in a vertebral direction—evidence of enlargement of both right and left ventricles, and right auricle. A choc en dome is perceptible in the sixth intercostal space at the left anterior axillary line. A systolic impulse and diastolic impact are palpable over the conus arteriosus of the right ventricle. *Murmurs or Murmurs* Upper. At the third intercostal space in the left midclavicular line. Right. Extends two-thirds of the way to the right midclavicular line in the fourth intercostal space. Left. Reaches the anterior axillary line in the sixth intercostal space. *Auscultation* At the apex, the systolic sound is accompanied by a loud, low pitched murmur, the diastolic sound is faint, with no adventitious sounds in diastole. At the aortic area, the systolic sound is accompanied by a murmur of less intensity than at the apex, the diastolic sound is accentuated and has a tympanitic quality, and is accompanied by a long murmur in diastole.

Arteries General sclerosis. The peripheral pulse is celer in type, monocrotic, it is grossly irregular and arrhythmic—the pulse of auricular fibrillation. Blood pressure 210/95.

Veins Tremendous engorgement in neck and arms.

Abdomen Large from obesity. No edema of wall, no free peritoneal fluid. The liver is enlarged and rotated extending three fingers' breadth below the right costal margin in the midclavicular line, it is tender, not increased in consistency. The spleen is enlarged to percussion, but is not palpable.

Laboratory Findings—Spinal fluid perfectly normal. Fluid from pleural cavity was a transudate. Urine showed albumin in varying amounts. Phenolphthalein excretion, 50 per cent in two hours.

Diagnosis—Primary sclerosis of the root of the aorta Insufficiency of the aortic valve, a result of rheumatic endocarditis Chronic myocardial disease, with very considerable enlargement of both ventricles, predominantly the left General arteriosclerosis

Treatment—Tincture of digitalis was given as follows

Date	Amount
October 15	15 cc
October 16	10 cc
November 6	15 cc
November 7	10 cc
November 19	15 cc
November 20	10 cc
November 28	8 cc
November 29	8 cc
December 2	5 cc
December 3	10 cc
December 4	8 cc

Total 114 cc

Course—Patient showed no great improvement at any time during his stay in the hospital He was discharged Dec 21, 1920, in practically the same condition as when he entered No electrocardiograms were made

Second Admission—Patient was readmitted to the hospital Jan 14, 1921 Since his discharge he had been constantly confined to bed His air hunger had not been so intense, but the abdomen had begun to swell conspicuously, and his output of urine had been very low The physical findings were much as before, except that there was more edema involving the lower extremities, the abdominal wall and the tissues over the sacrum, and there was evidence of greater stasis Patient's condition continued practically unchanged until Feb 17, 1921, when he suffered an acute dilatation of the heart The right auricle extended a finger's breadth to the right of the right midclavicular line, and the patient was in extremis Strophanthin, 0.65 mg, was administered intravenously without effect Removal of 600 cc of blood by venesection, and administration of an additional 0.15 mg of strophanthin, intramuscularly, was followed by immediate improvement in the patient's condition The right auricle receded to its original position, two-thirds of the way to the right midclavicular line The next day the patient was in better condition than he had been for weeks The remainder of his course was uneventful, and he was discharged April 21, 1921, in a somewhat improved condition

Electrocardiographic Record—Electrocardiograms were made at the time of the second admission, Jan 15, 1921 They showed simply auricular fibrillation with rather rapid ventricular rate, and preponderance of the levocardium Records made January 19, after the administration of 185 cc tincture of digitalis, again showed auricular fibrillation, but with a much slower ventricular rate No further records were made until April 14, 1921 In the meantime, the patient had had an acute dilatation of the heart, from which he made a good recovery, and had been thoroughly digitalized

Tincture digitalis was given as follows

Date	Amount
March 19	4 cc
March 20	8 cc
March 26	2 cc
March 27 to April 6, inclusive	33 cc
April 8 to April 11, inclusive	12 cc

Total 59 cc

It was noticed April 11 that the pulse rate had become exceedingly slow, and from auscultation one could detect coupling of beats, presumably a normal cycle with a premature contraction. It was when these phenomena were present that the last electrocardiograms were secured.

THE ELECTROCARDIOGRAMS

The records (Figs 1 to 6) show auricular fibrillation with a high degree of atrioventricular heart block. The block is probably not complete, however, for the interventricular intervals are not quite equal. The ventricle is still responding to supraventricular impulses. That the heart is strongly under the influence of digitalis is apparent from the coupling of a supraventricular cycle with a premature contraction of ventricular origin. The point to which I wish to draw particular attention is the changing character of the complexes which are responses to supraventricular impulses. The QRS and T deflections differ in a striking manner from cycle to cycle. The difference is manifest in contour, in direction of the deflection, in duration of the QRS interval, and in amplitude. Control curves are necessarily wanting, but it is certain that none of the complexes represents fully developed bundle branch block, and it is probable that none can be considered as a perfectly normal complex. Gradual and sudden transitions from levocardiogram to dextrocardiogram are seen, some complexes are polyphasic, others diphasic. It is my belief that these phenomena are due to unequally widened refractory periods of the right and left branches of the atrioventricular bundle. The supraventricular impulse is not transmitted through the two branches at the same rate at all times. If a stimulus enters at a time when the left branch is less refractory than the right the levocardiogram shapes the early portion of the complex, and the prolongation of the QRS interval and extent to which the curve becomes diphasic are proportional to the degree of difference in refractory periods. At one instant the levocardiogram precedes, at the next the dextrocardiogram precedes, again, they occur in normal time relation, and the result is a complex which closely approximates the normal.

The striking similarity between these curves and those published by Wilson and Herrmann¹⁰ is at once apparent. There are some differences, however. By comparison with other records made on this patient it is clear that the following complexes approximate the normal. For Lead I, Figure 1, strip I-1, cycle number 3, for Lead II, Figure 2, strip II-3, cycle number 3, for Lead III, Figure 3, strip III-3, cycle number 5. These complexes are marked with arrows in the figures. It will be seen that the fifth cycle in Figure 2, strip II-1 (marked with cross), is interposed between two complexes in one of which the levocardiogram predominates, in the other, the dextrocardiogram. The interposed complex, although intermediate in contour has a QRS

interval of only 0.055 second,¹¹ which is much shorter than 0.072 second, the approximate normal for this lead. A similar complex of even shorter QRS interval, 0.048 second, appears in Figure 2, strip II-4. In a heart in which conduction is known to be impaired, it is difficult to conceive of spread of the impulse to both ventricles in less than the normal time, and for this reason these two complexes defy analysis.

REVIEW OF THE LITERATURE

In my search of the literature I have been able to discover only eight cases which may properly be classified as examples of delayed conduction through both branches of the atrioventricular bundle. In

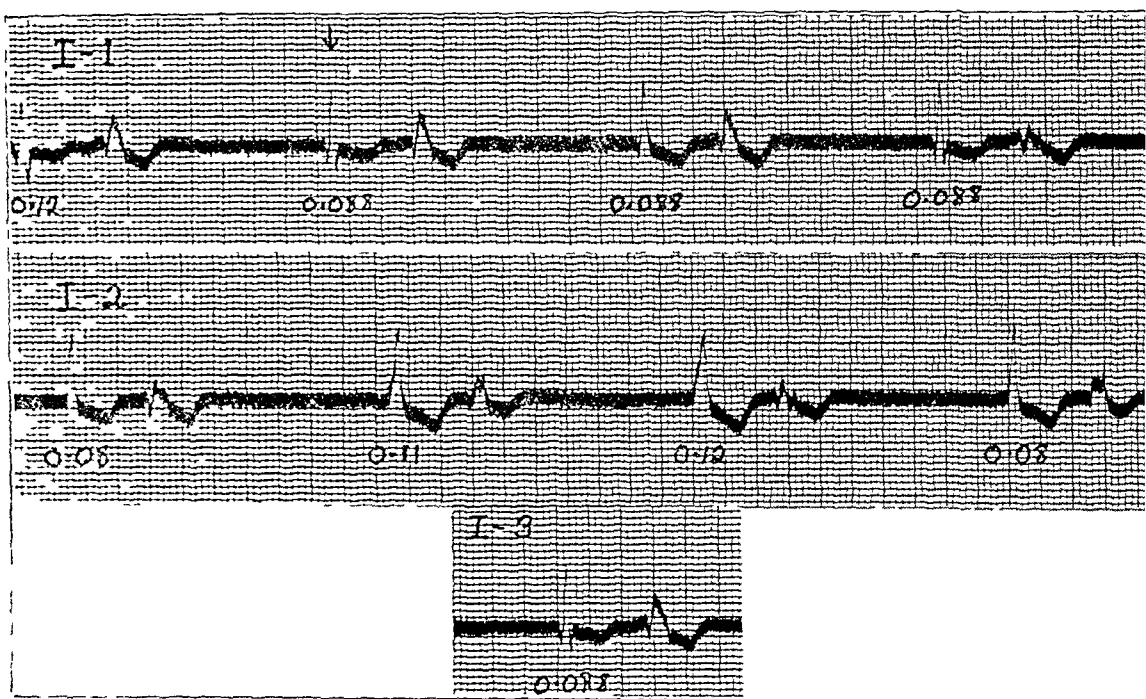


Fig 1—Lead I. In this, and in all succeeding figures, one division of abscissae equals 0.04 second, of ordinates, 10^4 volt, each strip is a direct continuation of its predecessor, within each lead, duration of QRS intervals is marked in seconds. For full description see text.

1911, and again in 1913, Cohn¹² described a case of complete atrioventricular heart block in a patient 70 years of age who was suffering from severe heart failure. In addition to the A-V block, the ventricular complexes show a great range of variation from dextrocardiogram to levocardigram. No normal complexes or fully developed bundle branch block complexes are shown. Cohn suggests that the varying complexes

¹¹ These measurements were made with a magnification of one hundred diameters, secured by lantern projection of the negatives upon coordinate paper ruled in millimeters. They are accurate within a few thousandths of a second.

¹² Cohn. Proc Soc Exper Biol & Med 9:24 1911, Heart 5:5, 1913.

are caused by functional depression of the bundle branches, possibly from digitalis, but he does not fully explain the transitional complexes. Mathewson,¹³ in 1913, described a case which showed both levocardiogram and dextrocardiogram, but no transitional complexes. In the same year, Oppenheimer and Williams¹⁴ placed on record an example of delayed conduction through both bundle branches showing many transitional complexes. Their patient also had complete A-V heart block. Necropsy revealed no pathologic changes in any part of the

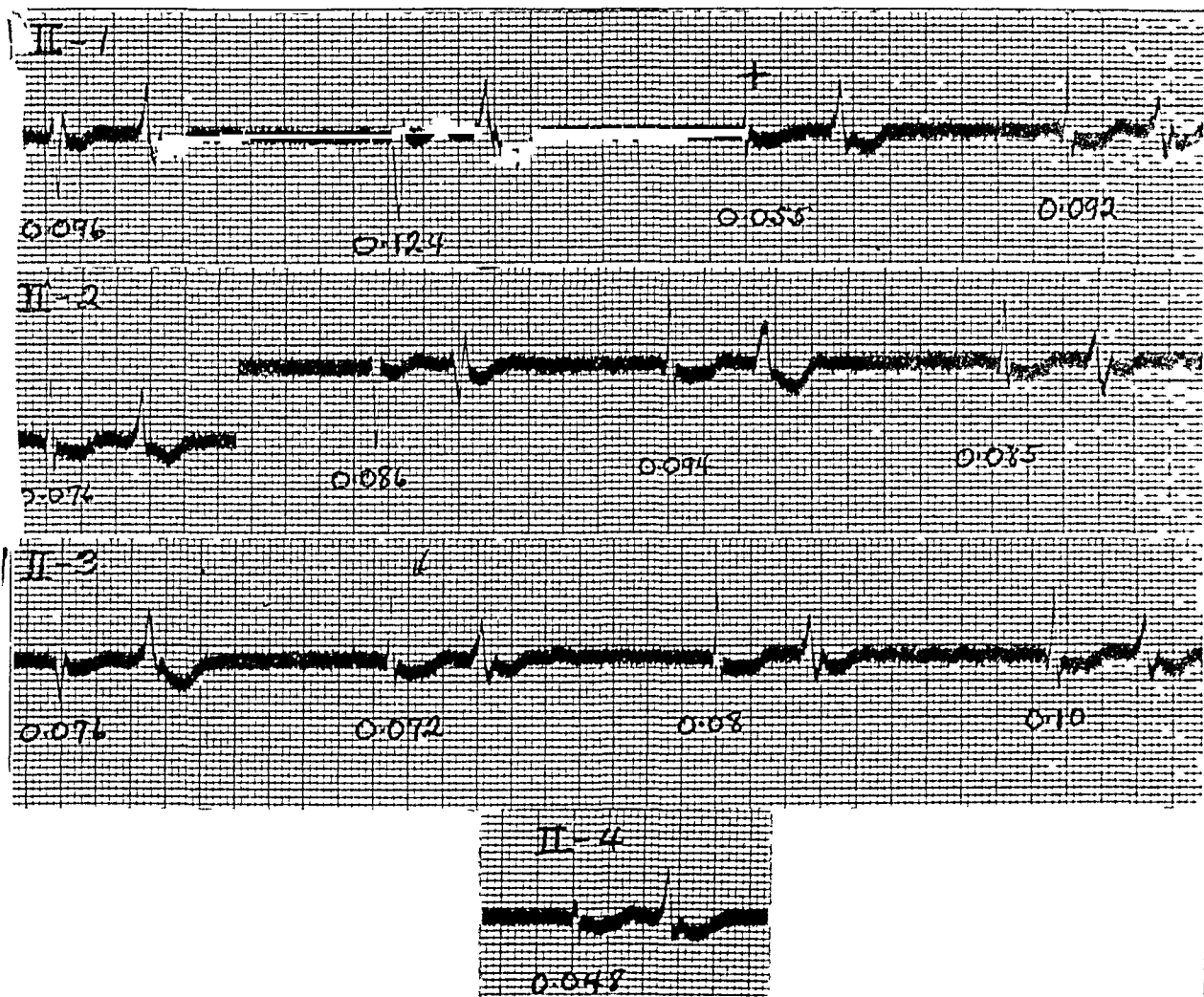


Fig 2—Lead II

conduction system. In 1915, Christian¹⁵ reported three cases, two of which were associated with an A-V heart block, one with auricular fibrillation. Necropsy in one case revealed no organic lesion of any part of the conduction system. Wilson and Robinson,¹⁶ in 1918, observed

13 Mathewson Heart 4 385, 1913

14 Oppenheimer and Williams Proc Soc Exper Biol & M 10 86 1913

15 Christian Arch Int Med 16 341 (Sept) 1915

16 Wilson and Robinson Arch Int Med 21 166 (Feb) 1918

delay in branch conduction, in a patient with complete A-V heart block, after a large dose of digitalis (Case 2, Fig 6, of their paper) In 1921, a case was reported from the clinic of White and Burwell¹⁷ which probably represents a much less degree of delayed branch conduction

Examples of delayed conduction through one branch only have been described by Wilson,¹⁸ Robinson,¹⁹ Mathewson,¹³ Frederica and Moller²⁰ and Wilson and Herrmann⁶

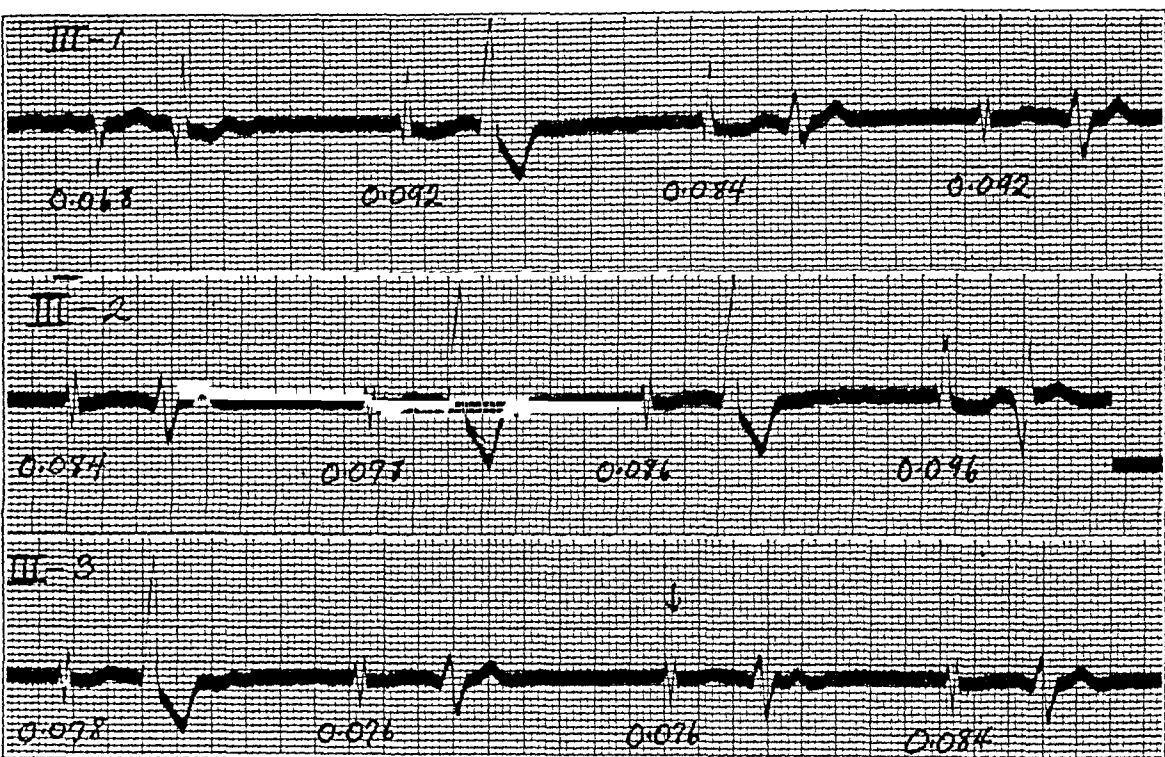


Fig 3—Lead III

CAUSE OF DELAYED BRANCH CONDUCTION

Exclusive of organic lesions, delayed conduction through the right and left branches of the atrioventricular bundle is clearly the result of disturbed relation between the rate at which impulses are discharged and the refractory periods of the A-V node and that of the individual branches, in which widening of the refractory periods of the branches plays the major part. It is obvious that delay in branch conduction of transmitted impulses cannot occur if the length of the refractory period

17 White and Burwell *Med Clinics N America* **4** 1839, 1921

18 Wilson *Arch Int Med* **16** 108 (July) 1915

19 Robinson *Arch Int Med* **18** 830 (Dec) 1916, *ibid* **24** 422 (Sept) 1919

20 Frederica and Moller Cited by Lewis, *Mechanism and Graphic Registration of the Heart Beat*, Shaw & Sons 1920



Fig 4—Lead III

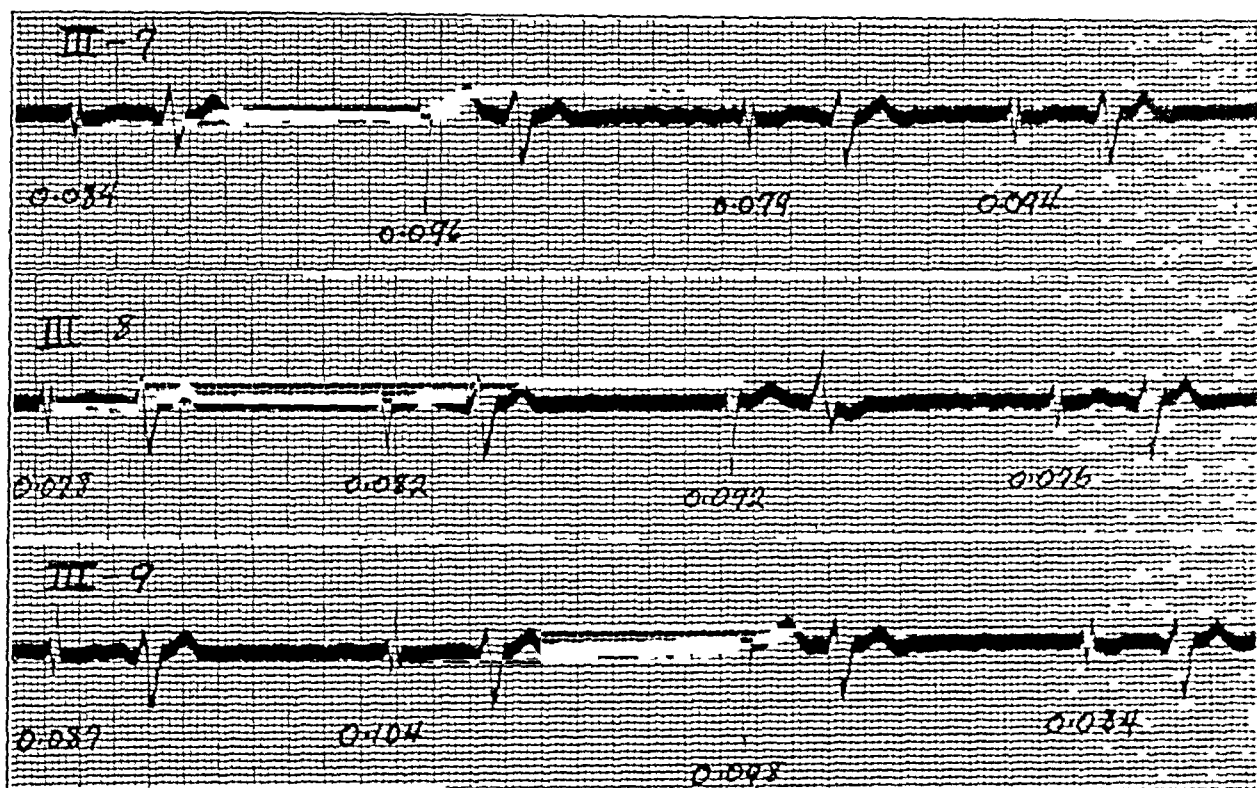


Fig 5—Lead III

of the A-V node exceeds that of the branches, regardless of the auricular rate. If the refractory period of either branch exceeds that of the A-V node however, delay in conduction through that branch must necessarily follow unless the auricular rate, in turn, is slow enough to permit full recovery of the branch after each beat. Deficient branch conduction is therefore due to widening of the refractory period of the branch in excess of that of the A-V node, coupled with a sufficiently high auricular rate. If delayed branch conduction occurs in conjunction with complete A-V heart block, it is due to the fact that the rate of discharge of impulses from the ventricular pacemaker is too high to allow full recovery of the branch after each beat. It is probable that the branch may be partially refractory, as well as absolutely refractory, and the degree of delay in branch conduction may depend upon how much of the required refractory interval has elapsed at the time the

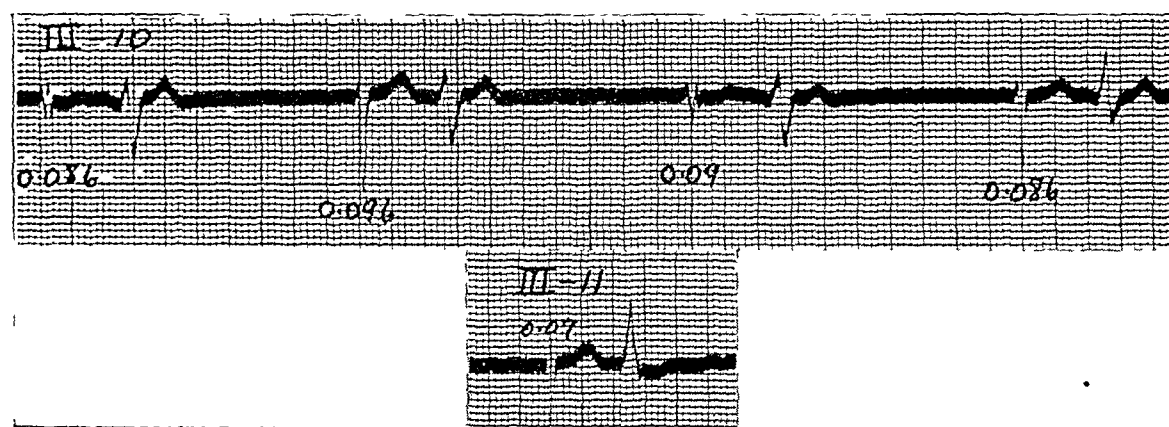


Fig 6—Lead III

new stimulus enters the branch. If the refractory periods of both branches are equal in length, and exceed that of the A-V node, the amount of delay will be uniform, but if the refractory intervals of the branches are of unequal length, the relative degree of delay in the two branches will vary constantly from cycle to cycle.

In clinical experience delayed branch conduction occurs either (1) spontaneously, or (2) as a result of digitalis intoxication. In the former instance it is no doubt due primarily to considerable impairment of the blood supply to the individual branches. The most brilliant examples of spontaneous occurrence are seen in the cases reported by Robinson¹⁹. One of his patients with auricular fibrillation and a rapid ventricular rate showed unmistakable evidence of delayed conduction through the right branch. After the refractory period of the A-V node had been lengthened by digitalis to a point where it equalled or exceeded the abnormally long refractory period of the right branch, the complexes became approximately normal. A few days

later, when the ventricular rate had increased fifteen beats per minute, evidence of delayed branch conduction again appeared *but only in those complexes preceded by a short diastole*. It is possible also that digitalis may directly shorten the refractory period of the branch in such cases by improving its blood supply. A review of other cases shows that the refractory period of the branch may be so long that that of the A-V node cannot be increased sufficiently by digitalis to compensate for it. Consequently, the rate at which transmitted impulses are received continues to be out of proportion to the lengthened refractory interval of the branch, and delay in conduction therefore persists until the refractory period is directly shortened, possibly by improvement in the nutrition of the branch.

When delayed branch conduction is not spontaneously present it may occasionally be produced by digitalis. Clinical evidence justifies us in advancing the suggestion that in certain cases where digitalis has been pushed strongly its action is exerted directly upon the individual branches of the atrioventricular bundle to such an extent that their refractory periods are prolonged to a degree in excess of the prolongation simultaneously produced at the A-V node, thereby delaying conduction through the branches. The condition is then identical in every way with that which occurs spontaneously. The electrocardiograms are such as have been described in my case report, they are in no way different from those occurring in deficient branch conduction which is not dependent upon drug action.

Cohn¹² is to be credited with this suggestion originally although he did not develop it completely. He ascribed the phenomena in his case to digitalis, although there was no other evidence that the patient had been under its influence. No mention of digitalis is made by Mathewson¹³ or Oppenheimer and Williams¹⁴. In the first three cases reported by Christian,¹⁵ and in the case reported by Wilson and Robinson,¹⁶ however, the relation is remarkably clear. In Christian's cases the varying ventricular complexes made their first appearance under digitalis, disappeared after discontinuance of the drug, and were again made to appear under digitalis. The varying complexes were always associated with a greater or less degree of atrioventricular heart block, and it is significant that they were last to appear under heavy doses of the drug, and first to vanish when it was withdrawn. As in my case, the heart in Christian's Case 1 was known to be strongly under the effect of digitalis, for in both cases the characteristic slow bigeminy appears. The second case described by Wilson and Robinson had complete atrioventricular heart block, but it was only after a massive dose (12 cc.) of tincture digitalis that his electrocardiograms displayed unmistakable signs of delayed branch conduction.

My patient was receiving the drug almost continuously from March 19 to April 11, at the end of which time a total of 59 c c had been taken. April 14 the records showing delayed branch conduction were secured. Unfortunately, it was impossible to secure further records after the effect of the drug had disappeared, for the patient suddenly left the hospital, and died June 6. The evidence in this case that delayed branch conduction was due to digitalis is, therefore, not so conclusive as it is in the cases of Christian and Wilson and Robinson, but it is nevertheless strongly suggestive.

The views here expressed concerning the nature of delayed branch conduction are closely in harmony either directly or by analogy with the recent work of Lewis and his associates,²¹ in which the earlier researches of Cushny²² have been largely confirmed and considerably amplified particularly with regard to the rôle played by high auricular rates in affecting degree of block at the A-V node.

SUMMARY

1 It is suggested that the older routine methods which have been depended on to show the normal and abnormal anatomy of the Purkinje system be subjected to rigid criticism. Recent work has made it clear that these methods have been inadequate.

2 Recent experimental work on the subject of delayed branch conduction is reviewed. A case is reported in which electrocardiograms parallel in a striking fashion those seen in experiments. Attention is directed to eight similar cases in the literature.

3 If the refractory period of the right or left branch of the atrio-ventricular bundle is longer than the refractory period of the A-V node, conduction through that branch is delayed provided the rate of impulse discharge from the ventricular pacemaker be sufficiently high. Digitalis may directly lengthen the refractory periods of the individual branches to a degree sufficient to produce delay in branch conduction.

21 Lewis, Drury, and Iliescu. *Heart* **9** 21, 1921.

22 Cushny. *J. Pharmacol. & Exper. Therap.* **11** 103, 1918.

STUDIES ON THE PHYSIOLOGY OF THE LIVER

III THE EFFECT OF ADMINISTRATION OF GLUCOSE IN THE CONDITION FOLLOWING TOTAL EXTIRPATION OF THE LIVER *

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ROCHESTER, MINN

In previous studies on the physiology of the liver,¹ a method of total extirpation of that organ and the effect of the removal on the sugar in the blood were recorded. Since, following removal of the liver the decrease in the blood sugar coincided so exactly with the development of the characteristic symptoms associated with the moribund condition, it was deemed highly possible that a causal relationship existed between the two. An investigation was made, therefore of the effect of the administration of glucose on animals in which the liver had been removed.

In order to obtain the normal blood sugar value, a specimen of blood was taken from the jugular vein of a dog in which the first two stages of the operation had been completed. The liver was then removed completely in the manner previously described, and close observations made. In many of the experiments the dog was allowed to develop the characteristic symptoms, and glucose was injected intravenously. In other experiments the glucose was administered either by os, by rectum, by jejunostomy, by continuous intravenous injection, or intraperitoneally immediately after hepatectomy, the general condition of the animal and its blood sugar were noted carefully.

The Effect of the Intravenous Injection of Glucose—The effect of intravenous injection of glucose on an animal dying from the removal of the liver is one of the most remarkable physiologic phenomena we have ever observed. The animal, comatose and perfectly flaccid, apparently unable to contract any muscle, except the diaphragm, is restored immediately to a seemingly normal condition by the injection of from 0.25 to 0.5 gm glucose for each kilogram of body weight. We have seen such animals stand thirty seconds after the injection of glucose, walk, respond to call, wag their tails, drink water, and so forth, in less than one minute from the time they had been perfectly flaccid. If the animal is allowed to develop the convulsions, which are quickly followed by death when untreated, the results are even

* From the Division of Experimental Surgery and Pathology, The Mayo Foundation, and the Section on Clinical Laboratories, Mayo Clinic.

1 Mann, F. C. Studies on the Physiology of the Liver. I. Technique and General Effects of Removal, *Am J M Sc* **161** 37 (Jan.) 1921. Mann, F. C. and Magath, T. B. The Effect of Total Removal of the Liver, *Tr Sect Path & Physiol, A M A*, 1921, p. 29.

more striking The convulsions stop immediately, consciousness returns, and in a minute or two the animal walks around normally Restoration to normal is usually possible by the injection of glucose at any stage of the moribund condition until the heart has actually stopped We have restored an animal after the cessation of respiration by maintaining artificial respiration until the glucose could be injected

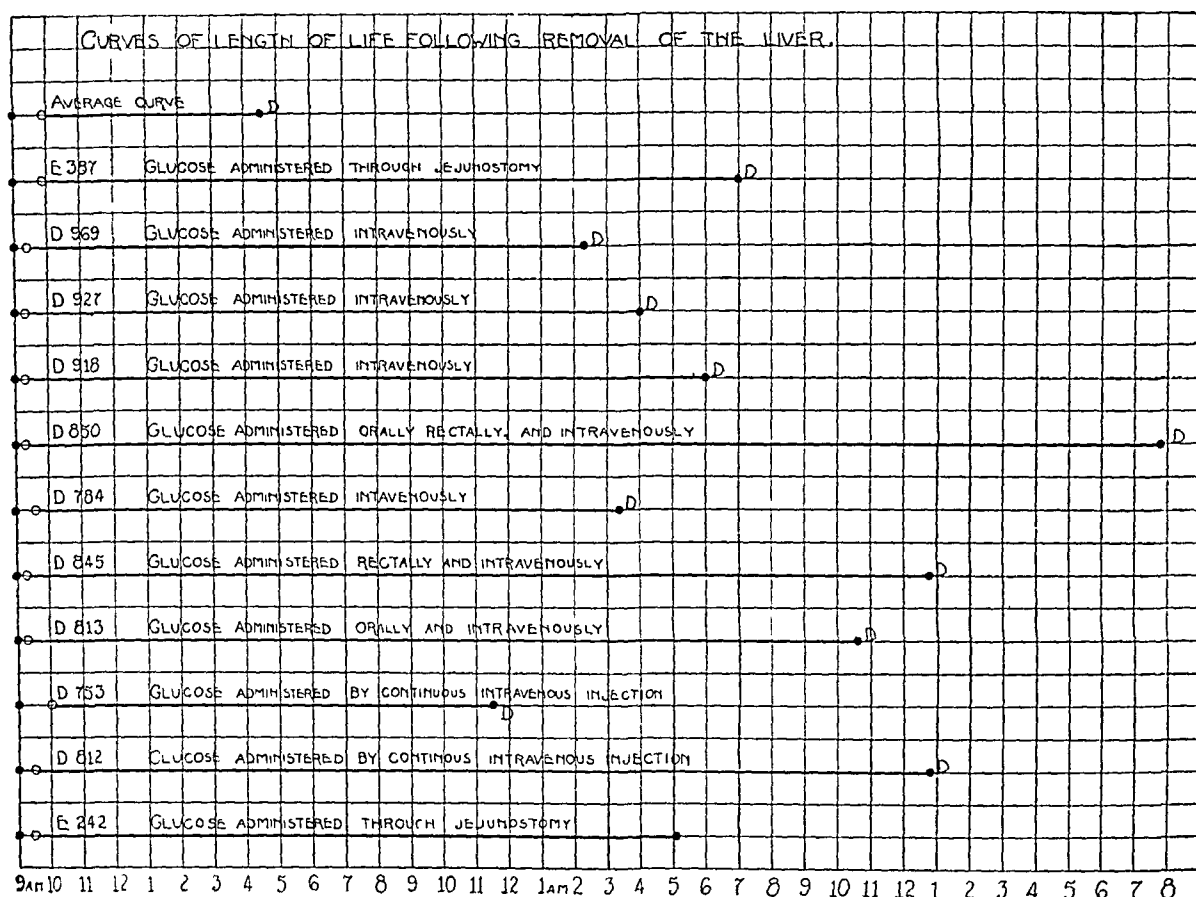


Fig 1—O Time of removal of liver D Time of death The first curve represents the average length of life in the average untreated hepatectomized animal The curve was constructed and the averages obtained from six animals dying from results of uncomplicated hepatectomy The second curve represents the length of life following removal of the livers of various animals after the administration of glucose Note the great increase in length of life due to the glucose administered

Immediately after the injection of glucose, the blood sugar reaches a very high level, at first it decreases quickly, then falls more slowly As the level again becomes low, the typical symptoms reappear The time this occurs after injection depends on many factors Some of these are the amount of glucose injected, whether the animal is active or quiet, and whether or not it is kept warm Restoration of the animal from the comatose condition can be repeated many times by the

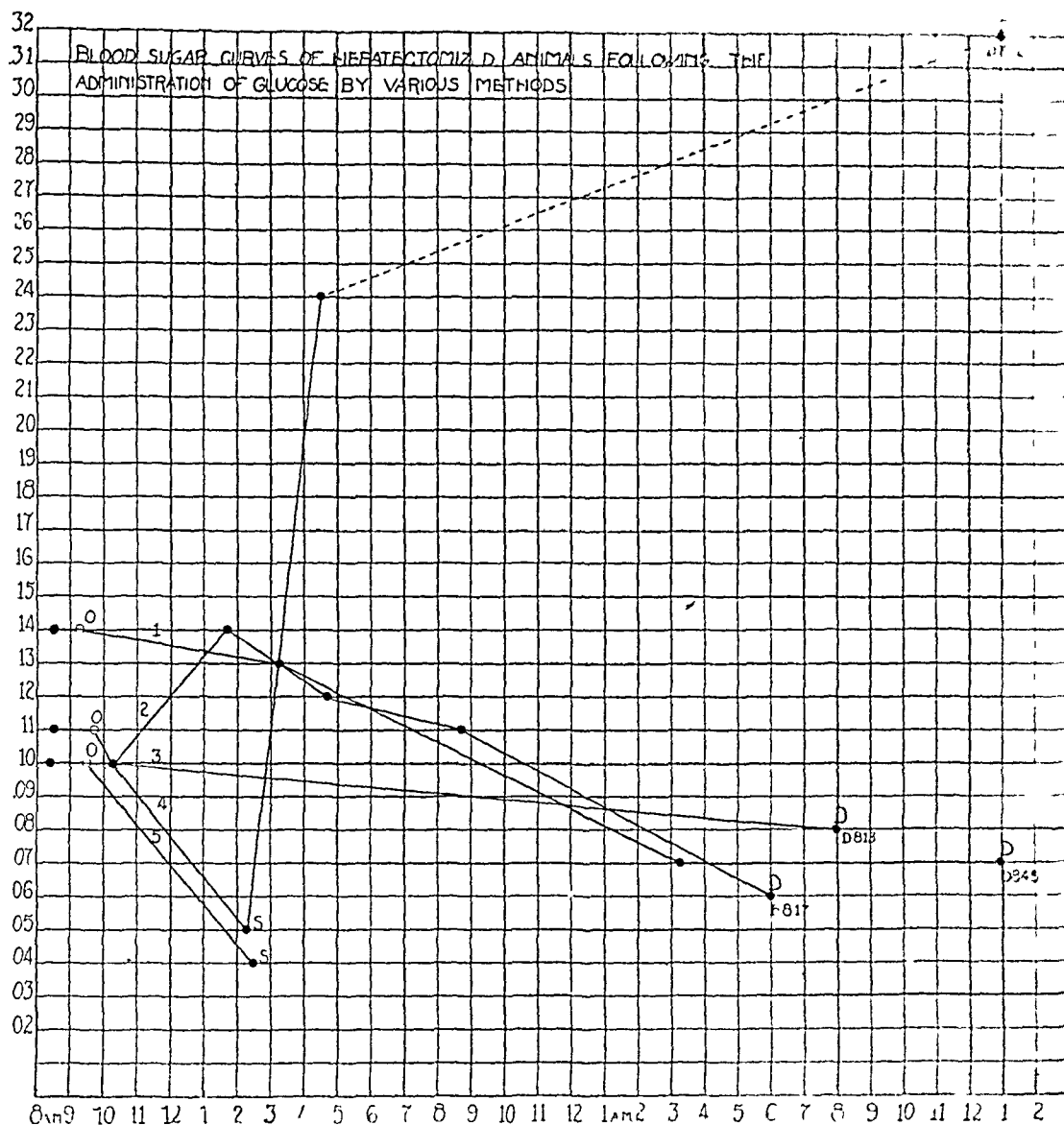


Fig 2—O Point of removal of liver S and D respectively Development of symptoms and death The first curve represents the blood sugar after the administration of glucose by rectum for many hours Absorption was not sufficient to maintain correct blood sugar level and glucose also was given intravenously for the last eight hours of the experiment The second curve represents the blood sugar after the administration of glucose through a jejunostomy, and the blood sugar level was maintained The third curve represents the blood sugar level during the administration of glucose orally and the blood sugar level was maintained throughout the experiment The fourth curve represents the blood sugar without the administration of glucose until the animal had developed the first symptoms when it was given intravenously The fifth curve illustrates the average course of blood sugar following removal of the liver Note the increase in the length of life when the blood sugar level was maintained at normal or above normal

injection of glucose. In each instance, its clinical condition exactly coincides with the blood sugar level. Finally, however, usually after many restorations, it may be noted that the same amount of glucose does not maintain the animal in a normal condition for so long a time and the characteristic symptoms develop at a higher blood sugar level.

The Character of the Symptoms that Develop with a High Blood Sugar Level After the Administration of Glucose—At this stage of the experiment another condition develops and other symptoms appear. These differ with different animals. In some experiments the animal suddenly becomes comatose and remains so for a variable period, usually not more than an hour, and dies suddenly and quietly. In

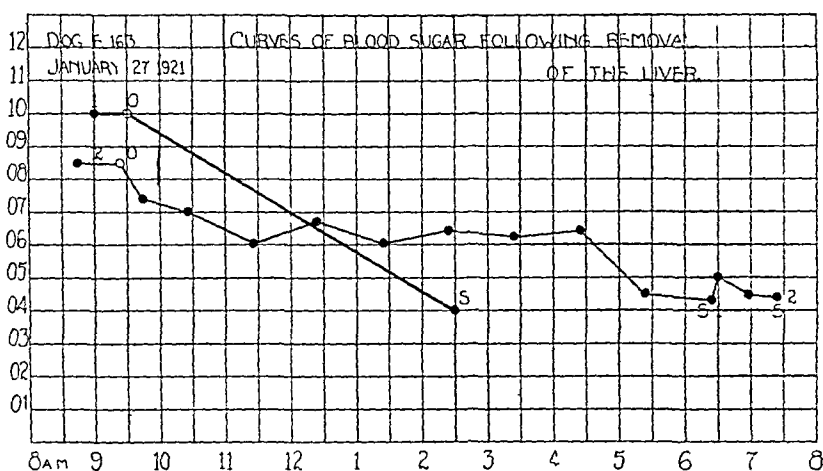


Fig. 3—The first curve shows the average change in blood sugar following removal of the liver. The second curve shows the gradual decrease in blood sugar of a dog kept very quiet after operation and artificial heat applied. O Liver removed. S, Animal moribund, 0.125 gm glucose for each kilogram of body weight was injected. This barely increased the blood sugar but restored the animal so that it could walk. This is the minimal amount of glucose which will produce a reaction when the animal is moribund.

other experiments the symptoms are similar to those following excessive feeding of meat to animals with Eck fistulas. The animal is at first quite restless, ataxia then appears, and sight and hearing are lost. Coma develops and death is sudden and quiet. Anuria usually accompanies this second moribund condition, the blood sugar level may be high and the injection of glucose is without beneficial effect.

The clinical appearance of the condition associated with low blood sugar and that with high blood sugar, is quite different. There is no difficulty in noting when the second condition is developing, but the rate at which it develops cannot be anticipated as it can in the first condition which is associated with a decrease in blood sugar. The cause of the second condition has not been determined, but it seems to be dependent on some change in metabolism other than carbohydrate

The Effect of Administration of Glucose by Continuous Intravenous Injection, Through the Alimentary Tract and Intraperitoneally—In some experiments, before the blood sugar had decreased to a low level and before symptoms occurred, glucose was injected slowly and at a fairly uniform rate with a continuous injection machine. In this manner the blood sugar level was kept normal or slightly above normal. The first group of symptoms never developed in these animals, but after from eighteen to twenty-four hours, the second group developed and the animals died.

In one series of experiments, an attempt was made to maintain the normal blood sugar level by the injection of glucose into the rectum.

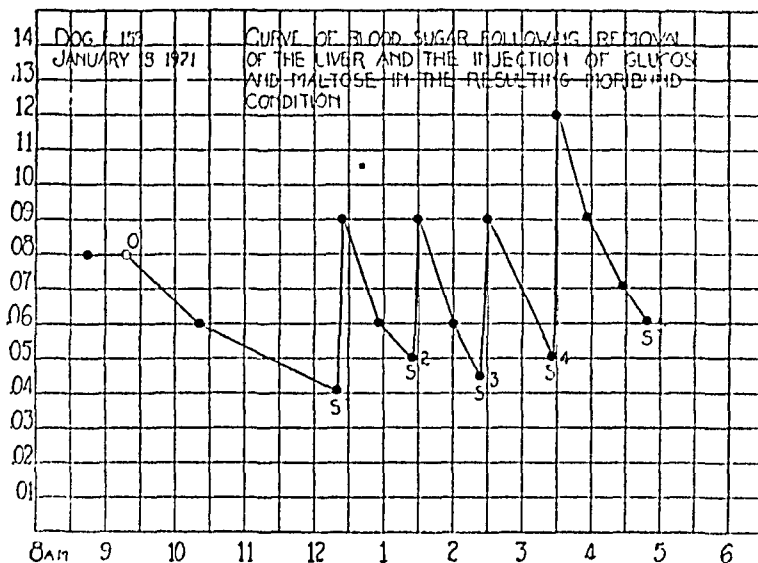


Fig 4—O Liver removed. Blood sugar which was rather low before operation decreased immediately and three hours after it was only 0.04 S₁. The animal was moribund, it was restored to normal by the injection of 0.25 gm glucose for each kilogram of body weight. S₂. After one hour when it was necessary to repeat the injection. S₃. Injection again repeated. S₄. At the end of the next hour symptoms developed and 0.25 gm maltose for each kilogram of body weight was injected. The maltose restored the animal in exactly the same manner as the glucose, except that the period of recovery was slower. Note the uniform rise in blood sugar following glucose injection, and that 0.25 gm for each kilogram of body weight appeared to last one hour.

In this we were only partially successful, because in many instances a considerable amount of injected fluid was rejected. However, the blood sugar level remained higher and the first group of symptoms appeared later than in animals not given glucose. In some cases enough glucose was absorbed so that the first group of symptoms did not develop but the animals died in from eighteen to twenty-four hours following the development of the second group of symptoms.

In some experiments the glucose was given by mouth, a few cubic centimeters of a weak solution, for example 10 per cent administered every few minutes beginning as soon as the animal recovered from

the immediate effects of the operation. These experiments were very successful so far as keeping the animal alive was concerned. In most cases the blood sugar was maintained at a normal level and the animal never developed the first group of symptoms, but died after the appearance of the second group. By a combination of oral and intravenous administration we were able to keep an animal alive thirty-four hours after complete removal of the liver.

The chief difficulty encountered with the oral administration was that the operative trauma sometimes interfered with the emptying of the stomach so that most of the glucose did not pass into the intestine where it could be absorbed. To obviate this a jejunostomy was made in some experiments at the time the liver was removed. The administration of glucose through a jejunostomy tube was the most satisfactory method used. We were able also to keep the blood sugar level normal by the intraperitoneal injection of glucose.

The Constancy of the Effect of Glucose—We observed the resuscitating action of glucose administered intravenously, more than 200 times in about forty hepatectomized animals. It never failed to restore to normal an animal that had developed the group of symptoms associated with low blood sugar. Further we administered glucose to twenty-five hepatectomized animals by the other methods mentioned, and in none in which we were successful in maintaining a normal blood sugar value or a hyperglycemia, did the first characteristic group of symptoms develop.

The Effect of Other Substances Administered—We attempted to determine whether the restorative action of glucose in the moribund condition following hepatectomy was specific. For this purpose a wide variety of substances which would seem to give some promise of having a related action, were tested in the same manner and in amounts which seemed to correspond to the amount of glucose necessary to restore the hepatectomized animal to normal. The following substances tested were found not to have a restorative action.

Saccharose, lactose, levulose, inulin, sodium chlorid, sodium sulphate, sodium carbonate, sodium bicarbonate, ethyl alcohol, glycerol, lactic acid (racemic), acetic acid, hydrochloric acid, pyruvic acid, epinephrin, pituitary extract, glycocoll.

Only four substances were found, besides glucose, which had a beneficial action when injected into the moribund animal with a low blood sugar following removal of the liver. These are maltose, mannose, dextrin and galactose.

The action of maltose is somewhat cumulative. When it is first injected in an animal with the characteristic symptoms following hepatectomy, the recovery is very slow but complete. Ten minutes may elapse between the time of injection and the time the animal

can walk, whereas when glucose is injected recovery is usually complete in from one to four minutes. When the animal becomes moribund again and maltose is again injected, the recovery is much faster than after the first injection. Mannose produces a response similar to maltose. Dextrin produces a definite but very slight beneficial action. The animal will probably regain consciousness and muscle tone but

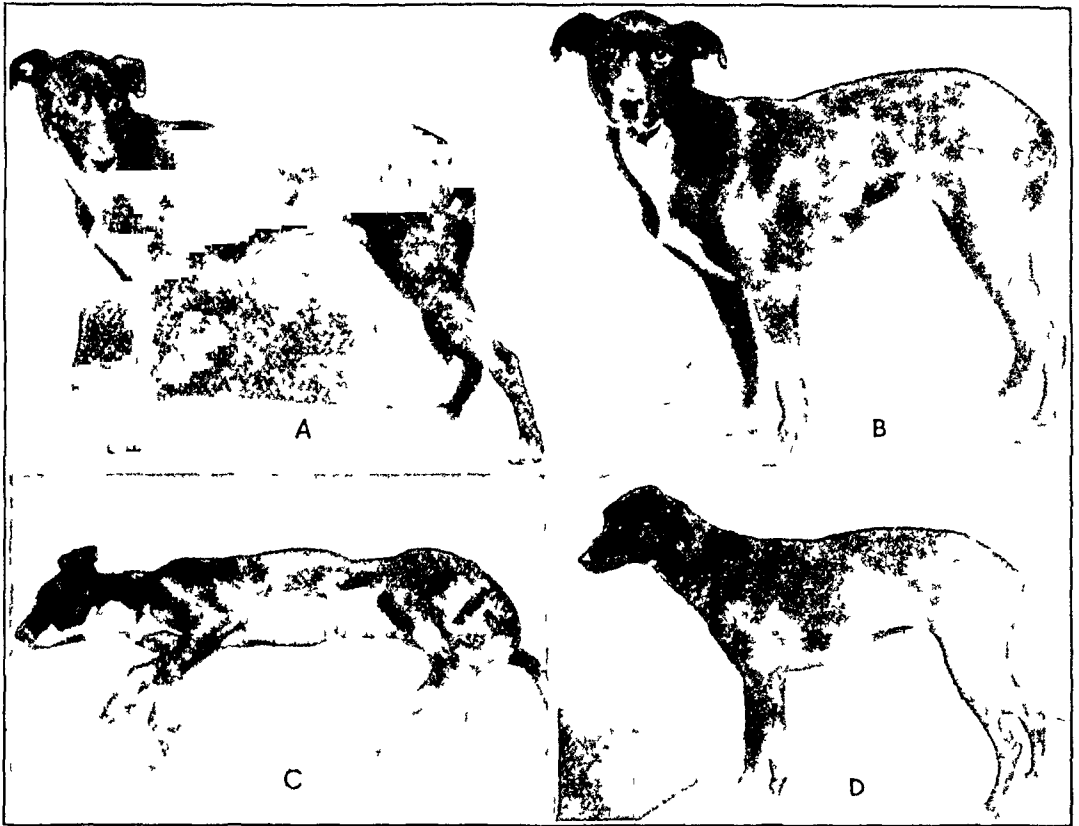


Fig 5—A Animal just preceding total removal of the liver. Two previous operations have been performed: (1) A reverse Eck fistula, (2) ligation of the portal vein. Blood sugar at this time, 0.10 per cent.

B Animal one hour after removal of the liver and less than two hours after the photograph shown in A. Note that the animal appears normal.

C Animal moribund, six and one-half hours following the total removal of the liver. The animal flaccid, with a few muscular twitchings. Without treatment this animal would probably have been dead within another hour. Blood sugar at this time, 0.05 per cent.

D Animal four minutes after the injection of glucose and five minutes after the picture shown in C. The animal again appears normal.

will not be able to stand when dextrin is injected. The beneficial action of galactose is so slight and transient that it would scarcely be noted unless the animal were under the strictest observation. While we have not determined why certain substances are beneficial in the restoration of an hepatectomized animal to normal it should be noted that maltose is supposed to be converted into glucose in the blood stream. If this is true, it explains the beneficial effect of maltose on hepatec-



Fig 6—A Kymograph record of respiration and blood pressure of an animal moribund for the first time following removal of the liver. Blood pressure 60. At Signal 1, 0.5 gm glucose for each kilogram of body weight was injected. The slight decrease in blood pressure is probably due to the rapid injection of a high concentration of glucose. Very little effect was produced on blood pressure but consciousness and muscle tone returned within three minutes.

B Kymograph of blood pressure of the moribund state several times by the injection of glucose. Blood pressure is very low (35), and the animal is in a very serious condition. At Signal 2, 0.5 gm glucose for each kilogram of body weight, was injected. The blood pressure increased from 35 to 70, and consciousness and muscle tone were also restored.

C Kymograph record of blood pressure and respiration of an animal moribund after total removal of the liver. Repeated injections of glucose had been made. The animal seemed to be dying when at Signal 1, 0.5 gm glucose for each kilogram of body weight was injected. The heart which stopped beating on the injection of this high concentration of glucose, slowly resumed its beat and blood pressure rose slightly. Consciousness and muscle tone returned a few minutes after the injection of glucose.

tomized dogs, and the release of excess maltose in the blood after the first injection explains the better and more prompt effect of the second. We suggest that mannose also may be changed into glucose in the blood stream. The beneficial effect of dextrin may be explained on the basis that it contains maltose and glucose as impurities.

The Amount of Glucose Necessary to Restore the Animal to Normal—While there has been individual variation in the reaction of the hepatectomized animal to various amounts of glucose, in general the quantitative relationship has been constant. The smallest amount of glucose which will produce a definite beneficial action in the moribund hepatectomized dog is 0.125 gm. for each kilogram of body weight. Smaller amounts than this usually do not produce noticeable effects, or produce questionable effects. One-eighth gram of glucose for each kilogram of body weight restores the animal to consciousness and enables it to stand, but not to regain its normal strength, and in a short time, from fifteen to thirty minutes, the comatose condition returns. When 0.25 gm. of glucose for each kilogram of body weight is injected, the recovery is prompt and complete. In our routine work we found that 0.5 gm. of glucose for each kilogram of body weight was the most satisfactory amount.

The Amount of Glucose Necessary to Maintain the Animal in a Normal Condition—The amount of glucose to keep the hepatectomized animal normal is subject also to individual variation, but on the whole is constant. In the average animal, kept quiet in a warm room, 0.25 gm. glucose for each kilogram of body weight maintains it for one hour. If the animal is flaccid and 0.25 gm. for each kilogram of body weight is injected intravenously, the animal will be restored to normal and will not need another injection for about an hour. Our routine injection of 0.5 gm. glucose for each kilogram of body weight usually was sufficient to maintain the animal for two hours. The effect of various experimental procedures, activity, and cold, often make it necessary to repeat the injections more frequently.

The General Effects of the Glucose Injection—The symptoms associated with the decreasing blood sugar following hepatectomy seem to show that at first there is a depression and later a stimulation of the central nervous system. We have not as yet determined definitely the nature of this process or the component parts of the nervous system acted on. In any event the injection of glucose abolishes completely all symptoms referable to the nervous system.

The effect of glucose injection on blood pressure depends on the condition of the latter at the time of injection. If the pressure is almost normal, as it is at the beginning of an experiment, the glucose causes but slight effect. If the pressure is low as occurs after an animal has been restored many times, the glucose causes a distinct rise in pressure.

The heart rate, which is usually very rapid after hepatectomy, may become slower when the blood sugar is very low. When the animal has developed well marked symptoms, it is usually irregular. The injection of glucose, regardless of the rate of heart beat produces a beneficial action, making it stronger and more regular. Electrocardiographic tracings have shown no change either when the animal was flaccid or after recovery following glucose injection.

In many of the experiments the irregularity of the respiration is marked. Following the glucose injection the respiratory movements return to normal.

The general temperature curve is downward throughout the course of an experiment. In some instances when this factor was observed closely, it rose slightly following glucose injection. In most experiments, the more rapid decrease in temperature occurred while the animal was moribund.

DISCUSSION

The explanation of the decrease in blood sugar following hepatectomy and of the remarkable restorative action of glucose when the animal seemed to be dying, is probably the same.² The chief possibilities in regard to this explanation were discussed in a previous paper.¹ Our further investigations enable us to elaborate on this discussion.

In view of the current idea that the liver is of great importance in regulating the reaction of the blood it was conceived that the removal of the organ might produce a condition either of alkalosis or acidosis, and that the glucose acted in some way to restore the hydrogen ion content of the blood. However, we have never found sufficient change in the hydrogen ion concentration or the carbon dioxide combining power of the blood at the time the first group of symptoms developed to warrant such a consideration. Furthermore, the injection of both acids and alkalis make the condition worse.

The action of glucose may also be explained by its osmotic power of changing the fluid concentration of the body cells and the composition and volume of the blood, thus washing out and diluting toxic substances which developed in the cells because of the absence of the liver. That this is not the manner by which glucose produces the remarkable effect is proved amply by the fact that other substances having even greater osmotic strength, such as hypertonic solutions of sodium sulphate and sodium chloride, do not produce beneficial action when injected in large amounts. The injection of other sugars such as levulose, saccharose, and lactose is of no value, while a weak

2. Mann, F. C., and Magath, T. B. Studies on the Physiology of the Liver II. Effect of Removal of the Liver on the Blood Sugar Level, *Arch. Int. Med.* 30: 73 (July) 1922.

solution of glucose restores to normal. A simpler explanation and one which agrees with most of our definitely proved facts, is as follows:

When the liver is removed a considerable proportion of the glucose storage capacity and the mechanism for elaboration of glucose is destroyed. The tissues use the sugar in the blood which for a variable period is partially maintained by the transformation into glucose of the available glycogen in the muscles. As the tissues utilize the glucose faster than it can be liberated from the muscles, blood sugar decreases as soon as the liver is removed. When the blood sugar has decreased below a certain amount, the concentration in the cells of the body becomes too low to maintain the normal cellular metabolism. This leads to the development of the characteristic symptoms described. The injection of glucose furnishes another food supply and cellular metabolism returns. While this is the most simple explanation of our facts, the final explanation will depend on the correlation with this of many other factors, for example the suddenness of the decrease in blood sugar.

The central nervous system seems to be early and markedly affected by the decrease in blood sugar. While the entire phenomenon which we have been studying can be referable to an effect on the central nervous system, at present it seems best to consider it a general bodily reaction.

SUMMARY

The total removal of the liver is followed by a definite and progressive decrease in blood sugar. Coordinate with this decreasing blood sugar, a characteristic group of symptoms develops. If glucose in suitable amounts is injected intravenously into an animal exhibiting these characteristic symptoms, it is immediately restored to normal. If glucose is administered so that the blood sugar does not decrease, the symptoms do not develop.

STUDIES OF CEREBROSPINAL FLUID AND BLOOD OF SYPHILITIC AND NORMAL PERSONS

WITH SPECIAL REFERENCE TO THE IMMUNITY REACTIONS AND
THE COLLOIDAL GOLD TEST ON THE ORIGINAL AND
ULTRAFILTERED FLUIDS AND SERUMS *

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The investigations reported in this paper have to do with various chemical, physical and immunologic studies of the cerebrospinal fluid and blood of syphilitics and nonsyphilitics and, also, with the factors concerned in the colloidal gold and the Wassermann reactions. The experiments fall more or less into two groups and so, for convenience in discussion, we have divided our paper into two parts. I Ultrafiltration of Syphilitic Serum, II The Substances Concerned in the Colloidal Gold Test and the Nature of the Reaction.

ULTRAFILTRATION OF SYPHILITIC SERUM

PART I

I INTRODUCTION

The nature of the active substance concerned in the Wassermann reaction has been discussed by many authors and numerous theories have been advanced as to the nature of this substance. Citron and Reicher¹ regarded it to be of a lipoid nature. Berczeller and Schilling² extracted syphilitic serum by ether and alcohol. The Wassermann reaction on the serum was weakened after extraction by ether but the Wassermann reaction was negative on the extract itself.

* From the Division of Nervous and Mental Diseases and the Department of Physiological Chemistry, University of Minnesota, Minneapolis. This work was done under a grant from the United States Interdepartmental Social Hygiene Board. We are indebted to Dr J F McClendon for many valuable suggestions and criticisms and to Dr S Marx White for unfailing interest and advice in the course of the work and the preparation of the paper.

¹ Part of the work presented in this paper was submitted as a thesis to the faculty of the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nervous and Mental Diseases, 1921 (C E N).

1 Citron and Reicher. Cited from Kolle and Wassermann, *Handbuch der pathogenen Mikroorganismen* 7 972, 1913.

2 Berczeller, L, and Schilling, L. Beitrag zur chemischen Untersuchung der Wassermannschen Reaktion, *Biochem Ztschr* 90 215 1918.

Wassermann³ divided the Wassermann reaction active substance into two parts. One of the parts was soluble in alcohol and the other was soluble in water. The former had a lipoid character and the latter contained protein. The Wassermann reaction on the alcoholic soluble substance was negative. The reaction of the mixture of the alcohol soluble substance and the water soluble substance was positive. The Wassermann reaction on the water soluble substance itself was positive. Schmidt⁴ claimed that the Wassermann reaction active substance was a globulin. According to this author the Wassermann reaction was also positive on globulin from normal serum but Bauer and Hirsch⁵ stated that the reaction was only positive on globulin from strong positive serum.

According to Felke,⁶ the Wassermann reaction was positive on albumin and he considered albumin to be the reaction substance. He separated globulin from albumin by hydrochloric acid but as globulin cannot be quantitatively precipitated by acid⁷ some globulin must, therefore, remain in the albumin fraction.

Scheer⁸ filtered syphilitic milk and syphilitic serum by ultrafiltration (3 per cent filtered). He found the Wassermann reaction to be negative on these ultrafiltrates. Egerer⁹ found the ultrafiltrates of syphilitic serums and spinal fluids to give weaker colloidal gold reactions than the originals.

In our experiments, syphilitic serum was filtered by the ultrafilter and the Wassermann reaction was done in the filtrates. The Wassermann reaction was also done on the globulin and albumin from normal and syphilitic serum, and the filtrability of globulin in syphilitic serum was compared with that in the normal serum. The globulin and albumin content of normal and syphilitic serum was estimated.

II METHODS

A Ultrafiltration—The apparatus for the ultrafiltration experiments was the one constructed for the experiments done by Egerer⁹ and was of the type described by Bechhold¹⁰. The inside of the apparatus was coated with tin and the net under the filter was coated with gold. This was done at the suggestion of Dr. Larson when we found that we were getting anticomplementary reactions on the filtrates.

3 Von Wassermann, A. Neue experimentelle Forschungen ueber Syphilis Berl klin Wchnschr **58** 193, 1921

4 Schmidt Ztschr f Hyg **69** 513, 1911

5 Bauer and Hirsch Wien klin Wchnschr **25** 155 1912

6 Felke, H. Die Rolle der Albumine und Globuline bei der Wassermannschen Reaktion, Munchen med Wchnschr **68** 1597, 1921

7 Hoppe-Seyler's Handbuch der Analyse, p 406

8 Scheer, K. Untersuchungen ueber die Sachs-Georgische Reaktion mit Milchluetischer Frauen, Ztschr f Immunitatsforschung **30** 178, 1920

9 Egerer To be published

10 Bechhold, H. Ultrafiltration, Biochem Ztschr **6** 379, 1907

Forty or fifteen pounds of pressure was used to filter the serum according to whether a 5 or 3 per cent coating was used in the ultra-filtration. Gun cotton was dried in the desiccator for a few weeks before the preparation of the collodium solution.

*B The Wassermann Reaction*¹¹—1 *Amoceptor* A rabbit was injected intravenously with 1 c.c. of sheep blood cell suspension every other day, five times in all. The rabbit was bled one week after the last injection and the hemolytic power of the serum was titrated. One-tenth cubic centimeter of the serum in the dilution (5 c.c. serum in 12 c.c. salt solution) was just enough to hemolyze 0.5 c.c. blood cell suspension with 0.06 c.c. guinea-pig serum in dilution (1 c.c. serum in 10 c.c. salt solution).

2 *Antigen* Twenty grams of human heart was put into 100 c.c. of absolute alcohol for ten days. Ten cubic centimeters of this extract was mixed with 9 c.c. salt solution. Four drops of 0.4 per cent alcoholic solution of cholesterol was added to the extract solution. One-tenth cubic centimeter of the antigen solution was used in the test.

3 *Sheep Blood Cells* Sheep blood was defibrinated by stirring with sterile wood sticks. The defibrinated blood was filtered by cotton and it was centrifugalized and washed with salt solution. This was repeated three times. One cubic centimeter of blood cells was suspended in 60 c.c. of 1.7 per cent salt solution, and 0.5 c.c. of this suspension was used for the test.

4 *Complement* One cubic centimeter guinea-pig serum was put into 10 c.c. of salt solution. Two minimum hemolytic units were used for the test. The units were estimated by the titration with amoceptor as follows. Of the guinea-pig serum diluted as stated, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09 and 0.1 c.c., respectively, was put into eight small test tubes and 1.5 c.c. salt solution, 0.5 c.c. blood cell suspension and 0.1 c.c. amoceptor serum was added to every tube. The tubes were left in the incubator at 37 C for one hour. The minimum hemolytic unit of the complement solution was determined by the amount necessary for complete hemolysis.

5 *Wassermann Test Proper* The serum to be tested was left in the thermostat at 65 C for thirty minutes. One drop of blood serum to be tested was put into the mixture of 1.5 c.c. salt solution, 0.1 c.c. antigen and two minimum hemolytic units of complement. This was left in the incubator at 37 C for one hour. After this period 0.1 c.c. of the amoceptor solution and 0.5 c.c. of the blood cell suspension was added to the mixture and it was kept in the incubator at 37 C.

¹¹ We are indebted to Dr. Larson, head of the department of Bacteriology, for the various reagents used in the Wassermann test.

for one hour again. Two control tests were made at the same time. One of them containing the hemolytic system and the antigen, but without the serum to be tested, the other control consisted of the hemolytic system with neither antigen nor serum to be tested. The tubes with the test, which were to be used for the test, were then centrifugalized. The degree of hemolysis was compared with the standard solution of hemoglobin.

This standard solution of hemoglobin was made by mixing 0.1, 0.2, 0.3, 0.4 and 0.5 c.c. of blood cell suspension, which was used for the Wassermann test, respectively, with 1.4, 1.3, 1.2, 1.1 and 1 c.c. of distilled water. The amount of hemoglobin in the last tube (0.5 c.c. blood cell suspension in 1 c.c. distilled water) is equal to that of the test when complete hemolysis took place or the Wassermann test was absolutely negative. The amount of hemoglobin in the first tube (0.1 c.c. blood cell suspension in 1.4 c.c. distilled water) is, therefore, equal to that in a test in which the degree of hemolysis is one fifth, or the Wassermann reaction is 80 per cent positive, and the dilutions above give comparisons for 80, 60, 40 and 20 per cent positive, and, as already stated, for complete negative, i. e., complete hemolysis.

6. Salt Solution. Nine-tenths per cent sodium chloride solution of a p_H 7.4 was used.

7. The influence of the H ion on the titration of complement was investigated. The experimental results were as follows.

The influence of H ion concentrations on the titration of complement was determined by changing the H ion concentrations from p_H 6.15 to p_H 8.4 with sodium bicarbonate.

Salt solution of varying p_H was used, the p_H of the blood cell suspension was 6.15 and this was kept constant in all experiments. The p_H of the medium in which the titration of complement was made is that of the mixture of the salt solution, blood cell suspension, amboceptor and complement. But the p_H which is noted in the following table is that of the mixture of salt solution and blood suspension.

The H ion concentration of the solution was determined by the colorimetric method. A phosphate mixture (of primary and secondary phosphate) and borax mixture (a mixture of borax and boric acid) was used as the standard solution. Phenol red (p_H 7.0—7.9), thymol blue (p_H 8.0—9.0) and brom cresol purple (p_H 5.6—6.6) were used as indicators.

In the titration were used 1.5 c.c. salt solution (0.9 per cent), 0.5 c.c. of 1.7 per cent blood cell suspension, from 0.01 to 0.1 c.c. of complement (diluted guinea-pig serum, 1.0 c.c. of serum plus 1.0 c.c. of salt solution) and 0.1 c.c. amboceptor (diluted immune rabbit serum, 0.3 c.c. serum plus 1.2 c.c. salt solution).

The effect of the H ion concentration on the complement was determined by comparing velocity of the hemolysis. The velocity of the hemolysis can be compared by measuring the amount of complement by which the hemolysis was completed in a certain time. If the amount of complement necessary to make the hemolysis complete is smaller, then the velocity of the hemolysis is greater. Therefore, we compared the velocity of hemolysis by measuring the reciprocal amount of the complement by which the hemolysis was completed in a certain time. Or, more accurately, estimations of the effect of H ion concentration can be obtained by comparing the velocity of hemolysis at various intervals. Therefore, the velocity of hemolysis was compared at fifteen, thirty, forty-five and sixty minutes. The sum of the reciprocal amount of the complement, by which the hemolysis was complete in fifteen, thirty, forty-five and sixty minutes was noted as the figure which is proportional to the velocity of the hemolysis. The results are noted in the accompanying tables.

The totals of the reciprocal amounts of complement necessary to complete hemolysis at fifteen, thirty, forty-five and sixty minutes in a group of three experiments are shown in Table 4, the p_H varying from 6.15 to 8.4.

The velocity in the same experiments at sixty minutes alone is shown in Table 5.

CONCLUSIONS

1. If we compare the velocity of hemolysis at fifteen, thirty, forty-five and sixty minutes, the velocity at p_H 8.15 is the greatest and it decreases in both directions from this point.

2. If we compare the velocity of hemolysis at sixty minutes alone the influence of p_H , except at p_H 6.15 and p_H 8.4, on the velocity of hemolysis is not so remarkable, as compared at fifteen, thirty and forty-five minutes.

3. Therefore, if the titration was made by measuring the amount of complement by which the hemolysis was complete at sixty minutes, the p_H of the solution can be changed between 6.5 and 8.15, without making any notable difference on the results of the test.

C Estimation of Globulin and Albumin—The Ross-Jones test was used in making the globulin determinations and the nitric acid test was used for noting the presence of albumin. Before the nitric acid test was made on the serum, the serum was made globulin free by precipitation with ammonium sulphate in half saturation and filtration. The numbers give the highest dilution of the serum in which the globulin or albumin test was positive, and, therefore, are proportional to the amounts of globulin and albumin respectively.

TABLE 1—VELOCITY OF HEMOLYSIS WITH p_H 7.55*

		Complement, in C c								
		0.02	0.03	0.04	0.05	0.05	0.07	0.08	0.09	1.0
15 minutes	Hemolysis	—	—	—	—	—	—	—	—	±
30 minutes	Hemolysis	—	—	—	±	±	+	+	+	+
45 minutes	Hemolysis	—	—	—	±	+	+	+	+	—
60 minutes	Hemolysis	—	—	+	+	+	+	+	+	+

+ = Complete hemolysis, ± = partial hemolysis, — = no hemolysis

TABLE 2—VELOCITY OF HEMOLYSIS WITH p_H 8.15

		Complement, in C c								
		0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	1.0
15 minutes	Hemolysis	—	—	—	—	—	—	±	±	±
30 minutes	Hemolysis	—	—	—	±	+	+	+	+	+
45 minutes	Hemolysis	—	—	±	+	+	+	+	+	+
60 minutes	Hemolysis	—	—	+	+	+	+	+	+	+

TABLE 3—VELOCITY OF HEMOLYSIS WITH RECIPROCAL AMOUNT
OF COMPLEMENT $\left\{ \frac{I}{C} \right\}$

	p_H 7.55	p_H 8.15
15 minutes	0	0
30 minutes	14.2	16.6
45 minutes	16.6	20.0
60 minutes	25.0	25.0

TABLE 4—RECIPROCAL AMOUNTS OF COMPLEMENT NECESSARY
TO COMPLETE HEMOLYSIS

Velocity of the Hemolysis	p_H					
	6.15	6.5	7.15	7.55	8.15	8.4
Experiment 1	67.2	90.1	90.1	100.0	104.6	78.2
Experiment 2	80.4	88.0	91.2	100.0	127.8	93.8
Experiment 3	73.8	89.0	89.0	100.0	140.7	65.8
	73.8	89.0	90.1	100.0	124.9	79.2

TABLE 5—VELOCITY OF HEMOLYSIS AT SIXTY MINUTES

Velocity of the Hemolysis	p_H					
	6.15	6.5	7.15	7.55	8.15	8.4
Experiment 1	75.0	100.0	100.0	100.0	100.0	60.0
Experiment 2	85.5	85.5	85.5	100.0	100.0	75.4
Experiment 3	80.1	100.0	100.0	100.0	100.0	66.8
	80.1	95.1	95.1	100.0	100.0	67.4

For example, if the highest dilution of serum giving a positive globulin test was 1 400 and the highest dilution giving an albumin test was 1 600, then the ratio of globulin to albumin would be as 400 600

The ratio of the content of globulin and albumin, which is shown in Table 6, is not the same as the actual ratio in the serum because the sensitivity on the globulin test and albumin test is not equal, but changes in the ratio of globulin and albumin can be determined by this method

D Dialysis of Serum—The collodion sac was used for the dialysis experiments The collodion solution was made by dissolving 25 gm collodion in 500 c c of a mixture of equal parts of ether and alcohol

E Preparation of Globulin and Albumin—Serum was diluted one half by distilled water and half saturated by the saturated ammonium sulphate solution The precipitate of globulin was separated from the solution by centrifugation The globulin was purified of salts by dialysis in the collodion sac in running tap water for two or three days The solution containing the albumin fraction was filtered and dialyzed in the same way The dialyzed albumin solution was filtered again and mixed with the same amount of 1 8 per cent salt solution

The globulin, which was dialyzed, was dissolved in a 0 9 per cent salt solution

III EXPERIMENTS

1 Wassermann Reaction on Dialyzed Serum, Globulin and Albumin

The Wassermann reaction was done on the dialyzed serum, globulin and albumin The positivity of the Wassermann reaction of the serum increased after dialyzation 14, 100 and 200 per cent, respectively, in the three cases of four experiments The positivity did not change in one experiment, in two other experiments the positivity of the reaction did not change but in these two tests the Wassermann reaction was 100 per cent positive before and after dialysis, the positivity of the Wassermann reaction of the serum after dialysis increased on an average of 78 5 per cent in four experiments

The Wassermann reaction on the globulin, which was separated from the serum, was done and compared with the reaction on the original serum The positivity on the globulin was increased 150 and 400 per cent, respectively, in two cases, it did not change in two experiments, in one case it was 60 per cent positive and in another case it was 100 per cent positive before and after the dialysis

In two cases it was decreased after the dialysis The decrease of the positivity of the reaction after the dialysis was 24 per cent in one case and 10 per cent in another

Hence, we can say that the Wassermann reaction on the globulin was positive after its separation from the serum

The Wassermann reaction on albumin was negative in five cases

The Wassermann reaction was done on the globulin, which was separated from the normal serum. The reaction was from 20 to 100 per cent positive, averaging 72 per cent positive in twenty-one cases.

2 Ratio of Globulin and Albumin in Normal and Syphilitic Serum
The Wassermann reaction was done on serum from normal and syphilitic patients and the ratio of globulin and albumin in these

TABLE 6—WASSERMANN REACTION ON SYPHILITIC SERUM, DIALYZED SERUM, GLOBULIN AND ALBUMIN

No		Dilution of Solution	Drops	Days of Dialysis	Wasser- mann Reaction	Per- centage Positive	Change After Dialysis
No 1							
	Original serum		1		+	100	
	Dialyzed serum	16 1	8	3	+	100	0
	Dialyzed globulin in salt solution	16 1	8	3	+	100	0
No 2							
	Original serum		1		+	70	
	Dialyzed serum	16 1	8	3	+	60	+14%
			16		+	80	
	Dialyzed globulin in salt solution	16 1	8	3	+	40	
			16		+	50	—24%
	Dialyzed albumin in salt solution	16 1	8	3	—	0	
			16		—	0	
No 3							
	Original serum		1		+	100	
	Dialyzed serum	12 1	6	3	+	80	
			12		+	100	
	Dialyzed globulin in salt solution	12 1	6	3	+	70	
			12		+	90	—10%
	Dialyzed albumin in salt solution	12 1	6	3	—	0	
			12		—	0	
No 4							
	Original serum		1		+	40	
	Dialyzed serum	24 1	24	3	+	80	+100%
	Dialyzed globulin in salt solution	14 1	14	3	+	100	+150%
	Dialyzed albumin in salt solution	14 1	14	3	—	0	0
No 5							
	Original serum		1		+	20	
	Dialyzed serum	12 1	12	3	+	60	+200%
	Dialyzed globulin in salt solution	12 1	12	3	+	100	+400%
	Dialyzed albumin in salt solution	14 1	14	3	—	0	0
No 6							
	Original serum		1		+	60	
	Dialyzed serum	16 1	8	2	+	50	
			16		+	60	0
	Dialyzed globulin in salt solution	16 1	8	2	+	50	0
			16		+	60	0
	Dialyzed albumin in salt solution	16 1	8	2	—	0	
			16		—	0	

various serums was determined. Table 8 gives the result of nineteen determinations of the globulin and albumin ratio and the Wassermann reaction and in addition shows the result of six experiments in which the concentration of serum was changed.

From the study of Table 8, it is evident that neither the actual nor the relative amounts of globulin and albumin is the essential factor in determining the positivity of the Wassermann reaction.

3 Filtrability of Syphilitic Antibody by Ultrafiltration (3 and 5 per cent) A syphilitic serum was filtered by 3 and 5 per cent ultrafilter The Wassermann reaction was done on the original and filtered serum Five of the fifteen filtrates by 3 per cent ultrafilter gave a

TABLE 7—WASSERMANN REACTION ON DIALYZED GLOBULIN FROM NORMAL SERUM

No	Concentration of Globulin	Drops	Wassermann Reaction on Dialyzed Globulin			Wassermann Reaction on Original Serum		
			Wassermann Reaction	Concentration of Globulin	Drops	Wassermann Reaction	Drop	Wassermann Reaction
1	Original	1	+70%	1 2	1	+65%	1	—
2	Original	1	+80%	1 2	1	+60%	1	—
3	Original	1	+60%	1 2	1	+50%	1	—
4	Original	1	+90%	1 2	1	+80%	1	—
5	Original	1	+70%	1 2	1	+65%	1	—
6	Original	1	+70%	1 2	1	+60%	1	—
7	Original	1	+80%	1 2	1	+60%	1	—
8	Original	1	+70%	1 2	1		1	—
9	Original	1	+60%				1	—
10	Original	7	+70%				1	—
11	Original	1	+70%				1	—
12	Original	1	+70%				1	—
13	Original	1	+70%				1	—
14	Original	1	+100%	1 2	1	+100%	1	—
15	Original	1	+100%	1 2	1	+100%	1	—
16	Original	1	+100%	1 2	1	+90%	1	—
17	1 4	4	+70%	1 4	8	+70%	1	—
18	1 4	4	+70%	1 4	8	+70%	1	—
19	1 3	3	+50%	1 4	6	+50%	1	—
20	1 4	4	+20%	1 4	8	+60%	1	—
21	1 4	4	+80%					

TABLE 8—WASSERMANN REACTION ON SYPHILITIC AND NORMAL SERUM AND ALBUMIN AND GLOBULIN CONTENT IN THE SERUM

No	Concentration of Serum	Globulin	Albumin	Ratio Between Globulin and Albumin	Wassermann Reaction, Percentage
1	1 1	1,600	3,200	1 2	+100
	1 2	800	1,600	1 2	+100
2	1 1	1,600	1,600	1 1	+100
	1 2	800	800	1 1	+100
3	1 1	1,600	1,600	1 1	+100
	1 2	800	800	1 1	+100
17	1 4	400	800	1 2	+ 90
	1 8	200	400	1 2	+ 80
18	1 4	400	400	1 1	+100
	1 8	200	200	1 1	+ 90
19	1 4	400	400	1 1	+100
	1 8	200	200	1 1	+100
4	1 1	1,600	1,600	1 1	+ 50
9	1 1	800	3,200	1 4	+100
10	1 1	1,600	3,200	1 2	+ 70
11	1 1	1,600	3,200	1 2	+ 30
12	1 1	800	1,600	1 2	+ 30
5	1 1	3,200	1,600	2 1	—
6	1 1	1,600	1,600	1 1	—
7	1 1	1,600	1,600	1 1	—
8	1 1	1,600	1,600	1 1	—
13	1 1	1,600	1,600	1 1	—
14	1 1	800	3,200	1 4	—
15	1 1	1,600	3,200	1 2	—
16	1 1	1,600	1,600	1 1	—

positive Wassermann reaction The filtrates by 5 per cent ultrafilter gave a negative Wassermann reaction in five cases

4 Globulin Content in the Original Serum and Filtered Serum The globulin content of the normal and original serum was com-

pared with that of filtered serum. The same was done on syphilitic serum. The filtrability of globulin in normal and syphilitic serum was compared. The same ultrafilter was used to compare the filtrability of globulin in normal serum with that of syphilitic serum. The serum was divided into two parts and these two samples from the same serum

TABLE 9—FILTRABILITY OF SYPHILITIC ANTIBODY BY ULTRAFILTRATION (3 PER CENT)

No	Wassermann Reaction			
	On Original Serum	Drop	On Filtered Serum	Drops
1	+	1	—	1
2	+	1	—	1
3	+	1	—	1
4	+	1	—	1
5	+	1	—	1
6	+	1	+	16
7	+	1	—	17
8	+	1	—	8
9	+	1	+	1
10	+	1	+	1
11	+	1	+	1
12	+	1	+	10
13	+	1	—	10
14	+	1	—	10
15	+	1	—	10

TABLE 10—FILTRABILITY OF SYPHILITIC ANTIBODY BY ULTRAFILTRATION (5 PER CENT)

No	Wassermann Reaction			
	On Original Serum	Drop	On Filtered Serum	Drops
1	+	1	—	10
2	+	1	—	10
3	+	1	—	10
4	+	1	—	10
5	+	1	—	10

TABLE 11—GLOBULIN CONTENT IN ORIGINAL AND FILTERED SERUM

No	Globulin		Ratio of Globulin in Original and Filtered Serum	Wassermann Reaction	
	In Original Serum	In Filtered Serum		Test	Control
1	1,600	4	400 1	+70%	—
	1,600	4	400 1	+70%	—
2	1,600	32	50 1	+30%	—
	1,600	16	100 1	+30%	—
3	1,600	80	20 1	+20%	—
	1,600	80	20 1	+20%	—
4	1,600	80	20 1	+20%	—
	1,600	80	20 1	+20%	—
5	800	10	80 1	+40%	—
	800	10	80 1	+40%	—
6	800	8	100 1	+50%	—
	800	8	100 1	+50%	—
7	800	16	50 1	+20%	—
	800	8	100 1	+20%	—

were filtered by the same filter one after the other. The filtrability of the globulin did not change by the second filtration through the same filter in five out of seven cases. The filtrability was decreased 1/2 by the second filtration by the same filter in two out of seven cases. The change of the filtrability 1/2 by the ultrafiltration is therefore within the scope of the technical failure of this method (Table 11)

TABLE 12—FILTRABILITY OF GLOBULIN IN NORMAL AND SYPHILITIC SERUM

No	Globulin			Wassermann Reaction on Original Serum	
	Original	Filtered	Ratio	Test	Control
1	1 600	40	40 1	—	—
	1 600	8	200 1	+	—
2	1,600	40	40 1	—	—
	1,600	40	40 1	—	—
3	1,600	40	40 1	—	—
	1,600	20	80 1	+	—
4	1,600	40	40 1	—	—
	1 600	10	160 1	+	—
5	1 600	32	50 1	—	—
	1,600	2	800 1	+	—
6	1,600	80	20 1	—	—
	1,600	20	80 1	+	—
7	1,600	160	10 1	—	—
	1 600	26	80 1	+	—
8	1 600	40	40 1	—	—
	1,600	8	200 1	+	—
9	3 200	160	20 1	—	—
	3,200	80	40 1	+	—
10	800	40	20 1	—	—
	3,200	40	80 1	+	—
11	1 600	160	10 1	—	—
	6,400	160	40 1	+	—
12	1 600	80	20 1	—	—
	1,600	20	80 1	+	—
13	1,600	80	20 1	—	—
	1,600	20	80 1	+	—
14	800	80	10 1	—	—
	800	10	80 1	+	—
15	3 200	160	20 1	—	—
	3,200	40	80 1	+	—
16	800	20	40 1	—	—
	3,200	4	800 1	+	—
17	1,600	32	50 1	—	—
	800	2	400 1	+	—

TABLE 13—FILTRABILITY OF GLOBULIN IN ORIGINAL AND FILTERED SERUM AND CHANGE OF FILTRABILITY IN SYPHILITIC SERUM

No	Ratio of Globulin in Original and Filtered Serum		Change of Filtrability of Globulin in Syphilitic Serum from That in the Normal Serum	
	Normal	Syphilitic		
1	40 1	200 1	—1 5	—4 20
2	40 1	40 1	1 1	
3	40 1	80 1	—1 2	
4	40 1	160 1	—1 4	—5 20
5	50 1	800 1	—1 8	—2 5 20
6	20 1	80 1	—1 4	—5 20
7	10 1	80 1	—1 8	—2 5 20
8	40 1	200 1	—1 5	—4 20
9	20 1	40 1	—1 2	
10	20 1	80 1	—1 4	—5 20
11	10 1	40 1	—1 4	—5 20
12	20 1	80 1	—1 4	—5 20
13	20 1	80 1	—1 4	—5 20
14	10 1	80 1	—1 8	—2 5 20
15	20 1	80 1	—1 4	—5 20
16	40 1	800 1	—1 20	—1 20
17	50 1	400 1	—1 8	—2 5 20

TABLE 14—FILTRATION OF SYPHILITIC SERUM BY 5 PER CENT ULTRAFILTER

No		Original Serum	Filtered Serum	Filtered Res	Change of Concentration of Globulin	Change of Wassermann Reaction
1	{ Wassermann reaction	+50%	—	+55%		
	{ Globulin	1 400	1 2	1 800	+2 1	+10%
	{ Drops	1	1	1		
2	{ Wassermann reaction	+20%	—	+20%		
	{ Globulin	1 400	1 80	1 1,600	+4 1	0
	{ Drops	1	1	1		
3	{ Wassermann reaction	+60%	—	+70%		
	{ Globulin	1 800	1 4	1 1 600	+2 1	+16%
	{ Drops	1	1	1		

The filtrability of globulin in normal serum was compared with that of syphilitic serum and the results are noted in Tables 12 and 13

The filtrability of globulin in syphilitic serum was not different from that in normal serum in three out of seventeen cases. In the other fourteen cases the filtrability of the globulin in the syphilitic serum was decreased 5–20 in the minimum and 1–20 in the maximum. The decrease in the average was 3.9–20. A change of 1–2 as has been noted is within the scope of the error of technic so that the decrease of the filtrability of the globulin in syphilitic serum from that in the normal serum may be estimated as about 1–2.5.

5 Concentration of Syphilitic Serum by Ultrafiltration. The decrease of filtrability of globulin in the syphilitic serum was noted and it was found that the Wassermann reaction active substance in the serum was held on the filter.

This result may be caused by the absorption of globulin and the Wassermann reaction active substance by the filter.

The filtrability of globulin in normal serum was then compared with that in syphilitic serum. The results are as given in Table 12.

6 The relation between the change of the concentration of globulin in the original and filtered serum and the change in degree of the Wassermann reaction was investigated. The Wassermann reaction 20, 50 and 60 per cent, respectively, positive serums were filtered through 5 per cent ultrafilter.

The concentration of globulin in the rest of the serum, which was held on the filter, was on the average increased 2.6–1 times from that in the original serum. The change of the concentration of globulin in the serum 2.6–1 was followed by the increase of the positivity of Wassermann reaction 0, 10 and 16 per cent, or 8.6 per cent in the average. In the one serum showing no increase in the positivity of the Wassermann reaction after filtration the test was only 20 per cent positive and may be regarded as a negative reaction. If we omit this serum, the change in the concentration of globulin in the serum 2–1 was followed by the increase of the positivity of the Wassermann reaction of 10 and 16 per cent, or 13 per cent in the average.

The relation between the change of concentration of globulin in the serum by the ultrafiltration and the change in the Wassermann reaction on the same serum was investigated in the above experiment.

The influence of the change of the concentration of globulin on the Wassermann reaction was determined, using globulin in salt solution.

A change in the concentration of the globulin of 2–1 was followed by an increase in the positivity of the Wassermann reaction from 10 to 50 per cent. In two cases a change of concentration of 4–1 was

TABLE 15—DILUTIONS OF GLOBULIN

Exper		Drops	Dilution	Wassermann Reaction		Change of Wassermann Reaction by Change of Concentration
				Test	Control	
1	Original serum	2	1 32	+20%	—	
	Globulin 1 1	2	1 32	+100%	—	25%
	Globulin 1 5	2	1 160	+80%	—	33%
	Globulin 1 10	2	1 320	+60%	—	50%
	Globulin 1 20	2	1 640	+40%	—	
2	Original serum	1	1 70	+100%	—	
	Globulin 1 1	1	1 70	+100%	—	100%
	Globulin 1 4	1	1 280	+50%	—	25%
	Globulin 1 8	1	1 360	+40%	—	
3	Original serum	1	1 70	+100%	—	
	Globulin 1 1	1	1 70	+100%	—	125%
	Globulin 1 4	1	1 280	+40%	—	0
	Globulin 1 8	1	1 360	+40%	—	33%
	Globulin 1 16	1	1 720	+30%	—	

TABLE 16—WASSERMANN REACTION OF DRIED SERUM

No	Original Serum			Suspension		Serum
	Dilution	Drops of Serum	Wassermann Reaction	Dilution	Drops	Wassermann Reaction
1	1 1	1	—	2 1	2	—
2	1 1	1	—	2 1	2	—
3	1 1	1	—	2 1	2	—
4	1 1	1	—	2 1	2	—
5	1 1	1	—	2 1	2	—
6	1 1	1	—	2 1	2	—
7	1 1	1	—	2 1	2	—
8	1 1	1	—	2 1	2	—
9	1 1	1	—	2 1	2	—
10	1 1	1	+40%	2 1	2	+20%
11	1 1	1	+70%	2 1	2	+20%
12	1 1	1	+70%	2 1	2	+30%
13	1 1	1	+100%	2 1	2	+30%
14	1 1	1	+100%	2 1	2	+30%
15	1 1	1	+100%	2 1	2	—

TABLE 17—WASSERMANN REACTION ON THE NORMAL SERUM WHICH WAS CONCENTRATED BY ULTRAFILTRATION

No	Serum	Concentration of Serum	Drop	Wassermann Reaction
1	Original		1	—
	Concentration	3 1	1	—
2	Original		1	—
	Concentration	5 1	1	—
3	Original		1	—
	Concentration	10 1	1	—
4	Original		1	—
	Concentration	6 1	1	—
5	Original		1	—
	Concentration	3 1	1	—
6	Original		1	—
	Concentration	6 1	1	—
7	Original		1	—
	Concentration	15 1	1	—
8	Original		1	—
	Concentration	14 1	1	—
9	Original		1	—
	Concentration	12 1	1	—

followed by an increase in the Wassermann reaction of 125 and 100 per cent, respectively. In Table 15 the globulin in each experiment is from the original serum and the ratios show the dilutions.

7 Wassermann Reaction on the Suspension of Dried Serum. One cubic centimeter of serum was put into a watch glass and dried on the water bath over boiling water. After drying, the serum was ground to powder in a small mortar. The powder was suspended in 1 c c of distilled water and the mortar was washed with 1 c c of salt solution. The salt solution which was used for washing was added to the suspension of the serum. The protein content of 2 c c of the suspension would, therefore, be equal to that of 1 c c of the original serum, and, therefore, 1 drop of the original serum was compared with 2 drops of the suspension for the Wassermann reaction test. The Wassermann reaction of the suspension of dried serum from normal blood was negative. The Wassermann reaction on dried syphilitic serum was weaker than that of the original syphilitic serum.

According to this experiment the Wassermann reaction active substance in the serum was partially destroyed by heating or drying (Table 16).

8 Wassermann Reaction on Normal Serum Concentrated by Ultrafiltration. A normal serum was filtered by 5 per cent ultrafilter. The serum remaining on the filter was concentrated from three to fourteen times in volume by the ultrafiltration.

The Wassermann reaction was negative on the concentrated normal serum in nine cases (Table 17).

IV REVIEW OF EXPERIMENTS

In our experiments the Wassermann reaction on the globulin from syphilitic and normal serum was positive and the Wassermann reaction on the albumin was negative. From this we may conclude that the Wassermann reaction active substance in the syphilitic serum is a globulin or is associated with the globulin. As has been shown by Schmidt¹ the globulin from normal serum also gave a positive Wassermann reaction. Schmidt explained the fact that globulin from normal serum gave a positive reaction while normal serum gave a negative reaction as being due to the protective action of the albumin. The explanation that suggests itself is that the globulin separated from normal serum may give a positive Wassermann reaction because of the fact that the physical or chemical condition of the globulin which has been separated from the serum by dialysis may not be the same as it is in the original serum and since the condition of the dialysed globulin from normal serum would be similar to the globulin dialysed from syphilitic serum we would expect a similar reaction in each case, and this has proved so in our experience, both giving positive Wasser-

mann reactions The condition of the globulin in syphilitic serum may be considered as similar to the condition of the globulin obtained by dialysis from normal serum We may further suppose that the condition of the globulin which was separated from syphilitic serum and dialyzed will not be the same as the globulin in the syphilitic serum, as the change has gone further in the same direction

The Wassermann reaction of the syphilitic serum was more strongly positive after dialysis than before Therefore it seems probable that the change of the condition of globulin in syphilitic serum is increased in the same direction by dialysis The ratio of globulin and albumin in normal and syphilitic serum was compared and it was found that neither the amount of globulin nor the ratio between globulin and albumin plays the essential rôle in the Wassermann reaction

Syphilitic serum was filtered by 3 and 5 per cent ultrafilter The Wassermann reaction active substance at times passed through 3 per cent ultrafilter and at other times did not The inconstant results could be caused by the difference of the positivity of the Wassermann reaction on the original syphilitic serum and by the unequal thickness of the ultrafilter

The Wassermann reaction active substance could not pass through 5 per cent ultrafilter

The Wassermann reaction was positive on the globulin and it was negative on albumin Therefore, it would seem that the Wassermann reaction active substance is contained in the globulin fraction

The filtrability of globulin in normal and syphilitic serum was compared by ultrafiltration The filtrability of globulin in syphilitic serum was decreased about 1.25 from that in normal serum Three explanations of this difference in the filtrability of globulin from normal and syphilitic serum may be given

- 1 Adsorption of globulin in syphilitic serum on the filter in greater amount than in the case of normal serum In reference to this we investigated whether adsorption of Wassermann reaction active substance does or does not take place The globulin in syphilitic serum was held back by the ultrafilter in greater degree than in normal serum A 2.1 change of concentration of globulin in syphilitic serum by ultrafiltration was followed by the increase of positivity of the Wassermann reaction by 13 per cent in the average The influence of the change of the concentration of globulin on the Wassermann reaction was also determined by using globulin in salt solution The change in the concentration of globulin by 2.1 was followed by a much greater increase of positivity of the Wassermann reaction than resulted from a similar change in concentration by ultrafiltration The positivity of the Wassermann reaction did not increase as expected in the proportion of the concentration of globulin in the syphilitic serum by ultra-

filtration If, as has been suggested, there is a Wassermann reaction active and negative globulin present in the syphilitic serum then, if the excess of the Wassermann reaction active globulin was adsorbed on the filter by the concentration of serum by ultrafiltration, the positivity of the Wassermann reaction does not change while the concentration of globulin may take place In our case the positivity of the Wassermann reaction was increased 13 per cent instead of the expected increase of 25 or 30 per cent From this we may conclude that one part of the Wassermann reaction active globulin was adsorbed on the ultrafilter and by this fact the decrease of the filtrability of globulin in syphilitic serum may be partially explained

2 The size of the globulin molecule in syphilitic serum may be larger than that in the normal serum and, if so, this would result in a decrease of filtrability of globulin in syphilitic serum The larger size of the globulin particle in syphilitic serum might be expected from the fact that the globulin in the normal serum was Wassermann reaction positive after dialysis and the size of the globulin was increased by dialysis We may consider the stronger Wassermann reaction and the larger size of the globulin particle as parallel phenomena

The size of the particle of globulin in the suspension of the dried serum should be larger than that of the original serum Nevertheless, the Wassermann reaction was weaker on suspension than that on the original serum, but this experiment is inconclusive as bearing on that point because of the fact that a change of chemical nature in the protein may take place during the process of heating

Hence, the size of the particle of globulin molecule, itself, alone, cannot be taken as the essential part for the positivity of Wasserman reaction A certain chemical nature of the particle is doubtless necessary for the reaction

3 By ultrafiltration the salts in the syphilitic serum can be taken out from the original serum, and, therefore, the concentration of salts in the original serum can be decreased by filtration On the contrary, the concentration of protein in the original serum was increased

The condition of the globulin in the serum can be changed by a change of concentration of salts in the same way as by dialysis

The decrease of filtrability of globulin in the syphilitic serum may be caused by the change of condition of the globulin by the decrease of salts through ultrafiltration and this changed condition will be similar to that of dialyzed serum, namely, the size of the particle of globulin was made larger by the decrease of the salt concentration

And, moreover, in that case it was supposed that the condition of globulin in the syphilitic serum can be changed easier than that in the normal serum

V SUMMARY

1 The globulin fraction in syphilitic serum contains the active substance in the Wassermann reaction

2 The filtrability of globulin in syphilitic serum by the ultrafilter was less than that in the normal serum

3 Three factors have been considered in this relationship (1) The possible ease of adsorption of the Wassermann reaction active globulin of the ultrafilter as compared with normal globulin, (2) the possible greater size of the particle of active globulin as compared with normal globulin, and (3) the possible instability of the active globulin as compared with normal globulin

PART II

THE SUBSTANCES CONCERNED IN THE COLLOIDAL GOLD TEST
AND THE NATURE OF THE REACTION

From the work of Thomas Graham on colloidal chemistry, about fifty years ago, there has been opened a vast and important field of investigation of the bodily processes in health and disease. The principles of colloidal chemistry were applied by Zsigmondy¹² to a study of the reaction of colloidal gold to certain colloids, especially proteins. He found that various proteins protected the colloidal gold against the coagulating effect of sodium chlorid, an electrolyte, there was also noted a variation in the protective power of different proteins, on this basis of relative protective action proteins were given numbers or values.

An extension and application of Zsigmondy's work to clinical use was made by Lange¹³ who discovered that normal and pathologic cerebrospinal fluids reacted differently on the colloidal gold. Because of Zsigmondy's investigations on the protective action of proteins, it is commonly stated in the literature that Lange's test depends on the protective power of the protein of the cerebrospinal fluid against the salt solution. The error of this conclusion is obvious, when one considers the fact that the amount of electrolyte used in the test is insufficient to produce precipitation of the colloidal gold and, therefore, the cerebrospinal fluid must play an active rôle in the production of the colloidal gold curve. In other words, pathologic cerebrospinal fluids must contain substances that have a coagulating effect on the colloidal gold.

12 Zsigmondy Die hochrothe Goldlösung als Reagens auf Colloide, Fresenius Ztschr f analytische Chem 40 697, 1901

13 Lange Die Ausflockung kolloidalen Goldes durch Cerebrospinalflüssigkeit beiluetischen Affektionen des Zentralnervensystem, Ztschr f Chemotherapie 1 44 1912

There has been considerable speculation and some experimentation on the nature of this reaction and the identity of the active substances Lange¹³ considered it as an indication of the mixture of the proteins Zaloziacki¹⁴ believed the reaction to be an immunity phenomenon

Jaeger and Goldstein¹⁵ regarded it as an indication of electrical changes in the fluid and, therefore, a physical phenomenon Eskuchen¹⁶ thought the cause of the precipitation to be due to the pathologic increase of the albumin, variations of precipitation are apparently caused by various forms of physiochemical relations of the albumin

Weston¹⁷ and Miller and his associates¹⁸ have found that the active substance in the cerebrospinal fluid was dialyzable, and the former concluded that globulin was the precipitating substance Felton¹⁹ said the zonal reactions are caused by the interrelationship of the globulin and albumin, the albumin protects and the globulin precipitates the gold

Cruickshank²⁰ isolated the globulin of paretic fluids and found the globulin to give a reduction in Zone I—a "paretic" curve In the study of dialysis of paretic fluids he found that the dialysates gave no change with colloidal gold He noted the protective action of cerebrospinal fluids by using sufficient strength of salt solution to entirely precipitate the colloidal gold He confirmed the work of Felton¹⁹ regarding the precipitating action of the globulin of pathologic fluid and the protective action of albumin, and states that the various types of reaction can be simulated by mixtures of globulin and albumin Since the "globulin obtained from negative spinal fluids, even when used in concentrated form, are almost inactive, the precipitating action of paretic fluids cannot be ascribed solely to the increase in globulin, but is probably dependent on a specific alteration of the physical state of the globulin, which is associated with a positive electric charge"

It is the opinion of McDonagh²¹ that the colloidal gold test occurs only when there are lipid globulin particles present, which are suitably

14 Zaloziacki Ueber den Eiweissgehalt der Zerebrospinalflüssigkeit, *Ztschr f Nerven* **47** 783, 1913

15 Jaeger and Goldstein Goldsolreaktion in Liquor cerebrospinalis, *Ztschr f d ges Neurol u Psychiat* **16** 219, 1913

16 Eskuchen Die funfte Reaktion, *Ztschr f d ges Neurol u Psychiat* **25** 486, 1914

17 Weston The Nature of the Substance Causing the Colloidal Gold Reaction, *Tr Am Psychol Assn* **26** 467, 1919

18 Miller, Brush, Hammers and Felton A Further Study of the Diagnostic Value of the Colloidal Gold Reaction, Together with a Method for the Preparation of the Reagent, *Bull Johns Hopkins Hosp* **26** 391, 1915

19 Felton Cerebrospinal Fluid and the Colloidal Gold Test, New York *M J* **105** 1170, 1917

20 Cruickshank The Value and Mechanism of the Colloidal Gold Test, *Brit J Exper Path* **1** 71, 1920

21 McDonagh Experiments with Cerebrospinal Fluid, *Lancet* **2** 991 (Nov 13) 1920

charged with hydrogen ions and that, although the reaction is electrolytic, it is influenced by the substratum (protein) to which the electrolytes are attached. He finds that nonelectrolytic lipid fails to precipitate the colloidal gold. "Therefore, may we say that the precipitation of colloidal gold is dependent on the protein particles, but that the action is started by the electrolytes attached thereto?"

From this summary of the literature it is evident that there is considerable diversity of opinion as to the nature and causes of the reaction. In an endeavor to throw further light on the mechanism of the colloidal gold reaction, we have studied the effect of syphilitic and nonsyphilitic globulins, albumin and dialyzed serums on the precipitation and protection of colloidal gold. We have also employed in this study the ultrafiltration of sera and cerebrospinal fluids and the estimation of globulin and albumin ratios.

The results obtained from various types of experiments will be given first with brief discussion. Detailed discussion and conclusions will follow the presentation of the experimental data.

TECHNIC

The method of preparing the colloidal gold and making the test was that described by Warwick and Nixon²². For the ultrafiltration studies, suggested by the work of McClendon²³, an apparatus similar to one described by Bechhold¹⁰ was used. The essential parts of this apparatus consist of an air pump and tank with gage for the compressed air and of the filtration chamber. The chamber is divided by a fine meshed gold coated screen, on which rests the coated filter paper. (This apparatus was used in the work of Egerer and the details of the apparatus and its use are described by Egerer in a paper to appear shortly.) In the dialysis experiments collodion sacs were used.

Relation of the Colloidal Gold Curve to Globulin—It is commonly observed in the clinical use of the colloidal gold test that there is no constant parallelism between the type curve and the amount of globulin as determined by the saturated ammonium sulphate solution ring test (Ross-Jones). It has also been noted by Solomon that a curve may be present with a negative Ross-Jones reaction. In a study of more than 800 spinal fluid examinations we have noted thirty-eight fluids giving definite curves, but giving a negative Ross-Jones test, the curves occurred in Zones I and II. There were four instances of a positive globulin test, with no changes in the colloidal gold.

22 Warwick and Nixon. A Study of the Colloidal Gold Reaction and Its Clinical Interpretation, Arch Int Med **25** 119 (Jan) 1920.

23 McClendon. The Formation and Composition of the Cerebrospinal Fluid J A M A **70** 977 (April 6) 1918.

Table 18 shows the curves obtained from globulin prepared from human blood serum by dialysis and separation from the albumin by precipitation with ammonium sulphate solution. Distilled water and physiologic solution of sodium chlorid were used as vehicles for the globulin, the amount of globulin in each case being the same in the salt and water, but not the same in different globulins.

TABLE 18—GLOBULIN CURVES

No		State	Colloidal Gold Curve
IV	Normal	In water pH 6.4	5 5 5 3 2 ± 0 0 0 0
		In salt pH 6.4	5 5 4 2 1 0 0 0 0 0
VII	Normal	In water	5 5 5 5 2 1 0 0 0 0
		In salt	2 5 5 4 3 1 0 0 0 0
VIII	Syphilitic	In water	5 5 5 5 5 5 3 1 0 0
		In salt	1 5 5 5 5 5 3 0 0 0
IX	Normal	In water	4 5 5 5 4 2 0 0 0 0
		In salt	5 5 5 5 3 1 0 0 0 0
X	Syphilitic	In water	4 5 5 5 5 2 ± 0 0 0 0
		In salt	5 5 5 5 3 1 ± 0 0 0 0
XI	Normal	In water	5 5 5 5 4 3 1 0 0 0
XII	Syphilitic	In water	2 4 5 5 5 5 4 3 1 0
1	In salt—from original (40 per cent)	14 times diluted, Was sermann 100 per cent on original serum	0 1 4 3 2 4 3 2 1
2	From normal serum diluted 4 times	In salt	0 1 3 5 5 5 2 1 0 0

The colloidal gold test was done on some globulin suspensions and solutions which were shaken little or not at all before using for the test (Table 19).

From these tables it is evident that globulin prepared from normal and syphilitic serums give distinct curves. The reduction usually

TABLE 19—GLOBULIN COLLOIDAL GOLD CURVE

No		State	Colloidal Gold Curve
III	Normal	In water	0 1 3 4 2 1 0 0 0 0
		In salt	4 4 3 2 1 0 0 0 0 0
V	Normal	In water pH 6.4	2 1 ± 0 0 0 0 0 0 0 0
		In salt pH 6.4	5 4 1 0 0 0 0 0 0 0
VI	Normal	In water pH 6.4	2 4 5 5 4 2 0 0 0 0
VII	Normal	In water	2 4 3 2 1 0 0 0 0 0 (See 7 in
		In salt	2 4 4 3 3 1 0 0 0 0 Table 18)
I	Normal	In water	1 2 3 5 5 5 4 3 1 ±
		In salt	0 1 2 5 5 5 5 3 1 0
II	Normal	In water	1 2 3 4 4 5 5 3 1 0
		In salt	0 1 2 3 3 4 3 3 1 0

occurs in Zone I though the greatest reaction may not take place in the first or second tubes.

Curves in Zone II are observed in the globulin preparations which were insufficiently shaken.

The globulins from syphilitic serums give somewhat more marked curves than those from normal sera.

Relation of the Colloidal Gold Curve to Albumin—The reactions in the colloidal gold test with albumin are noted in Table 20. The albumin was obtained from syphilitic and nonsyphilitic human serums. It is possible that our albumin solutions contain a trace of globulin but they were prepared with great care and all those noted in the following experiments gave a negative Ross-Jones test for globulin.

From Table 20 one may conclude that albumin from normal and syphilitic serums may cause a reduction in the colloidal gold, the curve occurs in the moderate dilutions.

Colloidal Gold Reaction with Dialyzed Serums—Table 21 shows the curves obtained with dialyzed and nonsyphilitic human serums. These serums give curves in the moderate and higher dilutions. The curves tend to be irregular.

Colloidal Gold Reaction with Ultrafiltrate of Syphilitic and Nonsyphilitic Sera—The colloidal gold test was done on the original and ultrafiltered serum. With few exceptions the curves were fairly similar and with the original serums occurred in the dilutions between 1:160 to 1:40,960. The ultrafiltrate gave reduction, commonly, in

TABLE 20—ALBUMIN CURVES

No		State	Colloidal Gold Test
III	Normal	In salt	0 0 ± 2 2 1 ± 0
XI	Normal	In salt	2 4 5 5 5 4 5 5 5 4 3 0
VIII	Syphilitic	In salt	0 ± 1 ± 0 0 0 0 0 0
X	Syphilitic	In salt	0 0 0 + 2 3 1 0 0 0 0
2	Normal	Diluted 4 times	0 0 0 ± 1 2 3 3 4 5 3 1 0 0 0 0
1	Syphilitic	Diluted 14 times, Was sermann negative	0 0 0 1 0 0 0 0 0 0

dilutions of from 1:80 to 1:10,240. There is a distinct moving of the curve to the lower dilutions by ultrafiltration, this phenomenon is somewhat more marked in syphilitic than nonsyphilitic serums (Table 22).

There is no constant difference in the curves of syphilitic and nonsyphilitic serums, but the syphilitic serums average a greater reduction than the nonsyphilitic serums.

Serums 75, 76 and 77 offer an interesting comparison. Serum 77, which is a nonsyphilitic serum, gives a strong curve, especially from the eighth to the fourteenth tubes, after ultrafiltration the curve is still very marked and reduction occurs in the first six tubes. Serum 75, from a syphilitic patient with a recently negative Wassermann test, gives a curve similar to, but stronger, than Serum 77, on ultrafiltration the curve is greatest in the lower dilutions, but extends over less dilutions than the ultrafiltrate or Serum 77. Serum 76, which gives a 100 per cent positive Wassermann reaction, shows a marked diminution of the curve by ultrafiltration, but what reduction there is occurs in the first tubes.

TABLE 21—DIALYZED SERUMS

No	State	Colloidal Gold Test
III	Normal	0 0 0 0 0 1 2 4 5 2 2 1 0 0
IV	Normal	0 0 1 2 3 4 1 2 4 5 3 0 0
V	Normal	0 0 0 1 3 2 1 4 5 5 3 1 2 1 0
1	Syphilitic, diluted 24 times, Wassermann 70 per cent	1 3 1 3 1 4 3 1 0 0 0

TABLE 22—ULTRAFILTRATE OF SYPHILITIC AND NONSYPHILITIC SERUMS *

No			Colloidal Gold Curve *	Globulin		
				Original	Filtered	Ratio
	Syphilitic	I	0 2 2 3 3 3 3 4 5 5	320	20	16
		II	0 1 2 3 4 4 4 4 4 4			
	Normal	I	0 0 0 0 0 0 0 0 1 2 5	320	40	8
		II	0 0 1 2 2 4 3 2 1 0			
10	Syphilitic	I	0 0 0 0 0 0 0 1 1 4 5 4 2	640	16	40
		II	0 0 0 1 3 4 3 0 0 0			
11	Normal	II	0 0 \pm 1 1 0 0 0 0 0			
12	Syphilitic	I	0 0 0 0 0 0 0 \pm 1 2 3 4 1 0 0	524	32	16
		II	0 0 0 1 2 3 3 1 0 0 0 0			
13	Wassermann negative	I	0 0 0 0 0 0 \pm 1 4 5 4 3 1 0 0	524	8	65
		II	0 0 \pm 1 1 2 2 2 4 4 2 0 0			
15	Syphilitic	I	0 0 0 0 0 0 \pm 1 2 3 5 3 1 \pm 0	524	8	32
		II	0 0 \pm 1 4 3 2 1 0 0 0 0 0			
16	Syphilitic	I	0 0 0 0 0 0 0 \pm 2 3 3 4 3 1 0	262	8	16
		II	0 0 0 \pm 1 2 3 4 3 1 0 0 0			
19	Syphilitic	I	0 0 0 \pm 1 2 2 2 3 5 5 4 2 1 1 0	524	32	8
		II	0 \pm 1 2 5 3 3 2 3 1 0 0 0			
18	Normal	I	0 0 0 0 \pm 1 2 3 3 3 3 4 4 3 1 0	524	64	4
		II	0 0 0 \pm 1 1 2 4 5 5 2 \pm 0 0			
17	Normal	I	0 0 0 0 0 1 1 2 2 3 4 5 5 2 1 0 0	524	128	4
		II	0 0 0 0 \pm 2 1 2 3 4 4 3 1 0 0			
21	Normal	I	0 0 0 0 0 1 2 3 3 3 3 4 3 2 1 0	256	64	4
		II	0 0 0 1 2 2 2 2 3 4 3 1 0 0 0			
22	Normal	I	0 0 0 0 0 0 1 2 2 3 3 4 3 \pm 0 0	256	54	4
		II	0 0 1 2 2 2 2 3 2 1 0 0 0			
23	Syphilitic	I	0 0 0 0 1 2 3 3 5 5 5 5 4 3 0 0	512	32	16
		II	0 0 2 4 4 3 2 1 0 0 0			
24	Syphilitic	I	0 0 0 0 1 4 4 3 4 3 4 4 4 3 2 1 0	256	8	32
		II	1 2 3 3 4 3 3 3 2 1 \pm 0 0			
25	Normal	I	0 0 0 0 1 2 3 3 3 3 4 4 3 2 1 0	1,024	256	4
		II	0 1 1 2 2 3 4 3 3 4 3 3 2 1 0 0			
26	Normal	I	0 0 0 1 0 1 2 2 2 2 4 3 3 1 0 0	1,024	256	4
		II	0 0 \pm 1 1 1 2 3 3 3 2 \pm 0			
27	Syphilitic	I	0 0 0 0 \pm 1 2 3 3 1 4 3 \pm 0 0	1,024	124	8
		II	0 0 0 \pm 1 1 2 3 3 3 2 1 0 0			
28	Syphilitic	I	0 0 0 0 0 1 1 2 2 2 3 5 4 2 \pm 0	512	32	16
		II	0 \pm 1 2 2 3 3 3 4 4 4 2 3			
31	Wassermann, 10 per cent	I	0 0 0 0 0 0 0 0 1 1 3 3 3 0 0	512	64	8
		II	0 0 \pm 0 0 \pm 1 1 1 \pm 0			
43		I	0 0 0 0 1 2 2 1 2 5 4 4 2 1 0	1,600	20	80
		II	1 5 5 5 5 4 2 1 0 0 0			
75	Syphilitic, Wassermann negative	I	0 0 0 0 0 2 5 5 5 5 5 5 5 3 1	1,600	32	50
		II	5 5 5 4 2 1 0 0			
76	Syphilitic, Wassermann 100 per cent	I	0 0 0 0 0 0 1 2 5 5 5 5 5 4	1,600	2	800
		II	4 2 0 0 0 0 0			
77	Normal	I	0 0 0 1 2 1 5 5 5 5 5 5 4 3 1	1,600	80	20
		II	5 5 5 5 5 5 0 0			
78	Wassermann, 60 per cent	I	0 0 0 0 1 1 1 2 5 5 5 5 5 2 1			
		II	5 5 5 5 5 4 1 0 0 0 0			

* The curves given in this and other tables are obtained by extending the dilutions, as made in the usual colloidal gold test, up to fifteen or more tubes as necessary, to reach the dilution at which no reduction occurs

TABLE 23—GLOBULIN AND ALBUMIN RATIO ON THE ORIGINAL AND ULTRAFILTERED SERUM

No	Wassermann Test			Original			Filtered			Globulin			Albumin			Colloidal Gold Test		
	Orig Inul	Fil- tered	Glob- ulin	Albu- min	Ratio	Glob- ulin	Albu- min	Ratio	Orig- inal	Fil- tered	Ratio	Orig- inal	Fil- tered	Ratio	Orig- inal	Filtered		
5	—	—	320	1,280	1 4	160	640	1 4	320	160	2 1	1,280	640	2 1	0 2 2 3 3 3 4 5 5	0 1 2 3 1 4 4 4 4		
9	—	—	640	1,280	1 2	16	32	1 2	640	16	40 1	1,280	32	40 1	0 0 0 0 0 0 0 1 2 3	0 0 1 2 2 4 3 2 1 0		
10	—	—	640	1,280	1 2	16	32	1 2	640	16	40 1	1,280	32	40 1	0 0 0 0 0 0 0 1 1 4 5 4 2	0 0 0 1 3 4 3 0 0 0		
25	—	—	1,024	1,024	1 1	256	512	1 2	1,024	256	4 1	1,024	512	2 1	0 0 0 0 0 0 1 1 2 3 4 4 3 1 0	0 0 0 0 1 1 2 3 3 3 2 1 0		
26	—	—	1,024	1,024	1 1	256	256	1 2	1,024	256	4 1	1,024	256	4 1	0 0 0 0 0 1 1 2 2 2 3 5 4 2 1 0	0 0 1 2 2 3 3 3 4 4 3 2		
27	+	+	1,024	4,096	1 4	124	512	1 4	1,024	124	8 1	4,096	512	8 1	0 0 0 0 0 0 1 1 1 2 3 3 4 4 3 1 0	0 0 0 0 1 1 2 3 3 3 2 1 0 0		
28	+	+	512	1,024	1 2	32	512	1 16	512	32	16 1	1,024	512	2 1	0 0 0 0 0 1 1 2 2 2 3 5 4 2 1 0	0 0 1 2 2 3 3 3 4 4 4 3 2		
29	—	—	1,024	2,048	1 2	256	512	1 2	1,024	256	4 1	2,048	512	4 1	0 0 0 0 0 1 0 1 0 1 2 1 0 0 0	4 4 5 5 2 1 1 1 1 1 1		
31	+10%	—	512	2,040	1 4	64	128	1 2	512	64	8 1	2,048	128	16 1	0 0 0 0 0 0 0 0 1 3 3 3 0 0	0 0 0 0 0 0 1 1 1 1 0		
32	+100%	+10%	512	1,024	1 2	16	128	1 8	512	16	32 1	1,024	128	8 1	0 0 0 0 0 0 0 1 1 2 3 3 3 2 1 0	0 0 0 0 1 1 2 3 3 2 0		

There are some noteworthy facts in the portion of Table 22 having to do with the globulin ratio. For example, Nos. 25 and 26 (ultrafiltrates) have the same amount of globulin, but the curves are distinctly different. Ultrafiltrate 26 has thirty-two times as much globulin as No. 24, yet the latter gives much the stronger curve.

Relation of the Globulin and Albumin Ratio to the Colloidal Gold Curve—Table 23 gives the ratio of globulin and albumin in the original and filtered serums as well as the proportion of each. It is notable that the curves vary distinctly, although the globulin to albumin ratio remains the same and even when the total albumin and the total globulin is the same in nonsyphilitic serums there is variation in the curve.

Serums 5, 9, 10, 26, 27 and 29 have the same ratio in each individual case between the globulin and the albumin in the original and ultrafiltrate. In the original serums the globulin albumin ratio is the same in Serums 5, 27 and 31 (1:4), in Serums 9, 10, 28 and 32 (1:2), in Serums 25 and 26 (1:1). In serums with the same ratio there is distinct variation in the curve, the same is true of the ultrafiltrates.

TABLE 24—ULTRAFILTRATION OF CEREBROSPINAL FLUID

Original	5	5	5	4	3	1	0	0	0	0
Ultrafiltrate	2	1	0	0	0	0	0	0	0	0
Original	0	0	0	0	0	0	0	0	0	0
Ultrafiltrate	0	0	0	0	0	0	0	0	0	0
Original	0	1	1	2	3	3	1	0	0	0
Ultrafiltrate	0	0	0	0	0	0	0	0	0	0
Original	0	0	0	0	1	3	5	5	5	3
Ultrafiltrate	3	2	1	0	0	0	0	0	0	0
Original	2	3	4	5	5	3	2	0	0	0
Ultrafiltrate	4	4	3	2	1	0	0	0	0	0

On the other hand, serums or ultrafiltrates with marked differences in the ratio may give similar curves, as, ultrafiltrates 26 and 27.

The same total amounts of globulin and albumin, as well as the same ratio, do not determine similar curves, as is noted on the original serums 31 and 32, and ultrafiltrates 9 and 10.

Ultrafiltrate 28 is interesting in that the globulin albumin ratio is 1:16, yet the colloidal gold reaction is stronger than in Serum 27, also a syphilitic serum, with a ratio of 1:4 or in Serum 10 with a ratio of 1:2.

From this table it is apparent that the globulin albumin ratio is not the determining factor in the colloidal gold curve, also that albumin, per se, does not tend to make negative curve.

Ultrafiltration of Cerebrospinal Fluid—A 3 per cent coating of the papers was used for the ultrafiltration of cerebrospinal fluid.

The ultrafiltration lessens the intensity of the curve and changes the zone of reduction to the tube of low dilution. A fluid giving a strong meningeal curve in the original gives a weak curve in Zone I after ultrafiltration (Table 24).

MISCELLANEOUS

In this group we include various unrelated experiments made with the purpose of noting the effect of various factors and conditions on the colloidal gold curve and also precipitin and anaphylactic tests with the cerebrospinal fluid

Additional amounts of the salt solution were used with cerebrospinal fluids, giving negative and positive curves. With the addition of 0.5 c.c. of 0.4 per cent sodium chlorid solution to each tube no curves were obtained in normal fluids, but in positive fluids the curves were intensified and tended to be more marked in the lower dilutions

(a) Usual method 0123310000

(b) Usual method—0.5 c.c. salt solution to each tube

	1233431000
a	0111000000
b	0111000000
a	0001310000
b	0001332100
a	0000110000
b	0001231000

Using 0.2 c.c. of equal parts of cerebrospinal fluid and water gave the following curve as compared with 0.2 c.c. of the undiluted fluid

Original	5555310000
Diluted	5543100000

The curve is similar but less extensive in the diluted fluid. Several experiments were done in which fluids giving similar or dissimilar curves were mixed in equal parts and allowed to evaporate, distilled water to the amount of one half the original volume of the mixture was added and the usual 0.2 c.c. of this was used in the colloidal gold test, this gave the same amount of the substances in the fluids as though 0.2 c.c. of each had been used. The curves from the original and mixed fluids were

Original Case C	5555310000
Original Case M	3444210000
Mixture	0013443100

In this instance the curve of the mixture is entirely unlike the original and is less marked

Original Case C	5555310000
Original Case B	1223210000
Mixture	1455555100

In this instance the mixture of a fluid with a weak curve with one giving a strong curve results in a different but more extensive curve than either of the originals

Globulin from a normal serum was diluted to the point where the globulin test was one faintly positive

3334554200

A dilution of three-fifths gave a reduction to "2" and a dilution of one-fifth to "3"

To 5 c c of colloidal gold 0.1 c c of normal globulin in water was added, giving a reduction to "2", when 1 c c of 0.4 per cent salt was added further color change to "3" occurred

A spinal fluid was boiled and filtered through ordinary filter paper

Original	5555431000
Filtered	0131100000
Original	2345532000
Filtered	0000000000

A mixture of albumin and globulin was made in the ratio of 2:1, in the test, therefore, two thirds as much albumin and one third as much globulin would be used as in the original tests

Original albumin	0001000000
Original globulin	1313143100
Mixture	0112343100

The curve is not markedly diminished by using only one third the amount of globulin and in spite of two thirds of supposedly protective albumin

In the first tube there was placed 0.2 c c cerebrospinal fluid "a," 0.04 c c albumin solution and 1.8 c c salt solution and dilutions made as usual

Original "a"	4455533200
Mixture	1223321000

This experiment was done using 0.02 c c albumin solution

1443321000

The albumin in this instance tends to diminish the curve and to change the zone of reduction

Protective Power of Cerebrospinal Fluid and Serum in Relation to Colloidal Gold Reaction—There are present in cerebrospinal fluid and blood certain substances which act in a protective way against the coagulation of colloidal gold by an electrolyte. In experiments having to do with the protective power of various substances sufficient amount of salt solution is used to entirely precipitate the gold. For this purpose 0.15 c c of a 10 per cent sodium chlorid solution was used with 2.5 c c of the colloidal gold solution

The protective power of cerebrospinal fluids, serums, globulins, albumins and ultrafiltrates of cerebrospinal fluids and serums was determined. It is recognized that the determinations are not absolute as the precipitating substance is also present and various amounts of the protective substance are required to neutralize the precipitating action.

REPORT OF EXPERIMENTS

In the following experiments the lower figure represents the degree of reduction in the colloidal gold as estimated in the usual colloidal gold test.

GLOBULIN								
	C c	C c	C c	C c	O c	O c		
In salt	0 01	0 005	0 0025	0 0012	0 0006			
Colloidal gold	1	3	5	5	5			
Syphilitic in water	0 15 0	0 1 0	0 05 0	0 03 1	0 02 1			
Normal in water	0 15 0	0 1 0	0 05 1	0 03 2	0 02 3	0 01 5		
IV in water	0 05 5	0 04 5	0 03 5					
VII in water	0 15 1	0 1 2						
VIII in water	0 15 0	0 1 3						
Normal in water	0 05 1	0 01 4	0 005 5	0 0025 5				
Syphilitic in salt	0 01 1	0 005 3	0 0025 5	0 0012 5				
Above globulin boiled and filtered through filter paper	0 01 2	0 005 5	0 0025 5	0 0012 5				
ALBUMIN								
Normal	0 02 0	0 01 1	0 005 1	0 0025 2	0 0012 4	0 0006 5		
Syphilitic	0 01 4	0 005 5	0 0025 5					
Syphilitic	0 01 0	0 005 2	0 0025 5	0 0012 5				
Syphilitic	0 05 0	0 04 0	0 03 0	0 02 1	0 01 3	0 005 5	0 0025 5	0 0012 5
Above boiled and filtered	0 04 0	0 03 0	0 02 0	0 01 1	0 005 3	0 0025 5	0 0012 5	
SERUMS I = ORIGINAL II = FILTRATE								
Normal	I 0 04 0	0 03 0	0 02 1	0 01 2				
Normal	I 0 012 0	0 006 0	0 003 1	0 0015 2				
Above	II 0 01 0	0 005 1	0 0025 2	0 0012 3	0 0006 4	0 0003 5		
Syphilitic	II 0 01 0	0 005 1	0 0025 2	0 0012 3	0 0006 4	0 0003 4	0 00015 5	0 00007 5
Syphilitic	I 0 II 2	0 2	0 3	1 4	1 4	3 5	4 5	
Syphilitic	I 0 II 1	0 5	0 5	0 5	1 1	1 3	3 5	
Normal	I 5	5						
Syphilitic	I 0	0	0	1	1	3		
Normal	II 0	1	2	3	4	5		
Syphilitic	I 0	0	0	1	2	3	5	

CEREBROSPINAL FLUID								
(Colloidal gold, negative)	0 06 0	0 05 0	0 04 0	0 03 1	0 02 3	0 01 5		
(Colloidal gold, 0 1 1 2 3 3 2 1 0 0)	0 06 0	0 05 0	0 04 0	0 03 0	0 02 0	0 01 1	0 0075 4	0 0032 5
(Colloidal gold, negative)	0 06 0	0 05 0	0 04 0	0 03 1	0 02 2	0 01 5		
(Colloidal gold, 5 5 5 5 4 2 1 0 0 0)	0 06 1	0 05 2	0 04 2	0 03 5	0 02 5			
(Colloidal gold, 2 3 4 4 3 3 2 0 0 0)	0 06 0	0 05 0	0 04 0	0 03 2	0 02 2	0 01 5		
(Colloidal gold, 5 5 5 5 4 3 1 0 0 0)	0 04 0	0 02 3	0 01 5					
(Colloidal gold, 0 1 2 4 4 3 1 0 0 0)	0 06 0	0 04 1	0 03 5	0 02 5				
Original cerebrospinal fluid	0 06 0	0 04 0	0 03 2	0 02 2	0 01 5			
Above with 0 05 c c glycerin to 1 c c cerebrospinal fluid	0	0	0	1	3			
Original with equal parts of 90 per cent alcohol filtered twice and alcohol evaporated	0	1	2	0 015 4	0 0075 5			
Ultrafiltrate	0 2 5	0 1 5	0 06 5					
(Colloidal gold, 2 3 4 5 5 3 2 0 0 0)	0 06 0	0 05 0	0 04 0	0 03 1	0 02 2	0 01 5		
Above ultrafiltrate	1 0 0	0 5 2	0 3 5	0 15 5				
(Colloidal gold, 4 4 3 2 1 0 0 0 0 0)								
Above original boiled and filtered	0 03 0	0 01 4	0 005 5					
(Colloidal gold, 0 0 0 0 0 0 0 0 0 0)								
Dementia paralytica, cerebro spinal fluid, ultrafiltrate	0 1 5	0 06 5						

Precipitin Test of Cerebrospinal Fluid—1 Precipitin test of spinal fluid with an antinormal human serum rabbit serum A rabbit was injected with 0 5 c c of a normal human serum intravenously Four days later the rabbit was injected again with 0 9 c c of a normal human serum intravenously Four, eight, seventeen, twenty-one and twenty-five days later, after the second injection, the rabbit was injected intraperitoneally with 1 5 c c, 2 0 c c, 0 5 c c, 1 0 c c and 2 c c, respectively The rabbit was bled seven days after the last injection

The titer of the immune serum was 1 2,948, that being the highest dilution of the normal human serum, which gave a definite precipitate with the mixture of the antihuman serum rabbit serum after two hours in an incubator at 38 C The precipitin test of the spinal fluid (normal spinal fluid, fluid from cases of dementia paralytica, cerebrospinal syphilis and tabes) with the antinormal human serum rabbit serum was done In one case the test was positive in the dilutions of 1 2, 1 32, 1 8 and 1 8 with the spinal fluid of normal, dementia paralytica, cerebrospinal syphilis and tabes, respectively, at the end of the second hour At the end of the third hour the test was positive in the dilution of 1 8, 1 32, 1 32 and 1 32, with the spinal fluid (normal, dementia paralytica, cerebrospinal syphilis and tabes), respectively

In another case the precipitin test of the spinal fluid (dementia paralytica, cerebrospinal syphilis and tabes) with the antinormal human serum rabbit serum was positive in the dilution of 1 32 for all the spinal fluids at the end of second and third hours

2 Precipitin test of spinal fluid with an antispinal fluid (dementia paralytica) rabbit serum A rabbit was injected with 2 c c spinal fluid from a case of dementia paralytica intravenously The rabbit was injected intravenously, with 4, 6 and 8 c c, respectively, three, seven and fifteen days after the first injection The rabbit was injected intraperitoneally with 2, 4 and 6 c c, of the spinal fluid from a case of dementia paralytica after fourteen, nineteen, and twenty-eight days, respectively, from the first intravenous injection The rabbit was bled eight days from the last intraperitoneal injection The titer of the immune serum was 1 512, which was the highest dilution of the spinal fluid of dementia paralytica, which gives a definite precipitate with the mixture of the immune serum after two hours in the incubator at 38 C

Precipitin test on spinal fluid (normal, dementia paralytica and tabes) with the antispinal fluid (dementia paralytica) rabbit serum was done

In one case the test was positive in the dilution of 1 32, 1 512 and 1 256 of the spinal fluid (normal, dementia paralytica and tabes) with the antispinal fluid (dementia paralytica) rabbit serum, respectively, at the end of the second hour

In another case the test was positive in the dilution of 1 256 and 1 128 on the spinal fluid (dementia paralytica and tabes) with the antispinal fluid (dementia paralytica) rabbit serum at the end of the second hour

Anaphylaxis Test with Syphilitic Cerebrospinal Fluid—Six guinea-pigs were sensitized with intraperitoneal injections of 1 c c of the cerebrospinal fluid from cases of dementia paralytica Twelve days later one of the sensitized guinea-pigs was tested by the intracranial injection of 0.5 c c of spinal fluid from a case of dementia paralytica There was no reaction Twenty-eight minutes later a second injection of the same amount was given, also with no reaction, and thirty-five minutes later a third injection of 0.5 c c was given intracranially still with no reaction The anaphylaxis test was then negative with 1.5 c c spinal fluid on the twelfth day after the sensitization of a guinea-pig by 1 c c of cerebrospinal fluid from a case of dementia paralytica On the sixteenth day one of the guinea-pigs was injected intracranially with 1 c c cerebrospinal fluid from a case of dementia paralytica The anaphylaxis test was also negative in this instance The third guinea-pig was taken from the sensitized group on the twenty second day and 0.5 c c of cerebrospinal fluid was injected intracranially In the first and second minute after injection there were strong convulsions Five

minutes later there was passing of feces. Seven minutes later the guinea-pig was biting the floor. Seven minutes later the guinea-pig was very calm. Twenty-seven minutes after the injection there was again passing of the feces, and forty-seven minutes after the guinea-pig appeared sick, but had no convulsion. The guinea-pig died the following day. The anaphylaxis test was, therefore, positive with 0.5 c.c. of dementia paralytica spinal fluid on the twenty-second day after the sensitization of the guinea-pig with 1 c.c. cerebrospinal fluid. On the twenty-fourth day another guinea-pig was injected intracranially with 0.8 c.c. of cerebrospinal fluid from a case of dementia paralytica. Six minutes after injection there was a strong convulsion. Eight minutes later there was opisthotonus. Ten minutes later the guinea-pig appeared relaxed and died eleven minutes after the injection. The anaphylaxis test was, therefore, strongly positive with 0.8 c.c. spinal fluid from a case of dementia paralytica on the twenty-fourth day after sensitization of the guinea-pig with 1 c.c. of such spinal fluid.

A normal guinea-pig was injected intracranially with 0.8 c.c. spinal fluid of dementia paralytica. Ten minutes later it was injected again with 1 c.c. of the same spinal fluid. There was no reaction after the injection in either case. Therefore, the anaphylaxis test was negative with 1.8 c.c. spinal fluid of dementia paralytica on the normal guinea-pig.

On the twenty-fourth day one of the guinea-pigs which was sensitized with spinal fluid of dementia paralytica was injected intracranially with 0.8 c.c. spinal fluid from a case of cerebrospinal syphilis. Eleven minutes later the guinea-pig was again injected intracranially with 0.7 c.c. spinal fluid from a case of cerebrospinal syphilis. The guinea-pig was sick after the injection in both cases, but had no convulsion. The anaphylaxis test was weakly positive with 1.5 c.c. spinal fluid from a case of cerebrospinal syphilis on the twenty-fourth day after sensitization of the guinea-pig with 1 c.c. spinal fluid of dementia paralytica.

Passive Anaphylaxis Test with a Spinal Fluid of Dementia Paralytica—A rabbit was injected intravenously with 0.5 c.c. spinal fluid and with 1, 2 and 2 c.c. spinal fluid intravenously on the fourth, seventh and tenth days, respectively, after the first injection. The rabbit was injected with 6, 6 and 8 c.c. spinal fluid from a case of general paralysis intraperitoneally on the fourteenth, seventeenth and twenty-first days, after the first injection. The rabbit was bled six days after the last injection. The titer of the serum was 1:256, which was the highest dilution of the spinal fluid of general paralysis that gives a definite precipitate with the immune rabbit serum in the mixture of the spinal fluid of general paralysis and the immune rabbit serum after one hour in an incubator at 38°C.

Five guinea-pigs were injected with 1 c c each of an antispinal fluid (general paralysis) rabbit serum intraperitoneally. Forty-eight hours later one of the guinea-pigs was injected with 0.4 c c spinal fluid of dementia paralytica. Eight minutes later the guinea-pig was injected with 0.6 c c of the same spinal fluid. Ten minutes later it was biting on the floor, but had no convulsion. Thirty-five minutes later it was still sick.

One of five guinea-pigs which were injected with immune serum forty-eight hours before, was injected intracranially with 1 c c of a spinal fluid from a case of dementia paralytica. Two minutes later there was a convulsion. Two minutes later the guinea-pig was biting on the floor. Seven minutes later the guinea-pig was injected with 0.5 c c of the spinal fluid. One hour later the guinea-pig was still sick but had no convulsion.

One of five guinea-pigs injected with immune serum forty-eight hours before was injected with 1 c c spinal fluid from a case of dementia paralytica intracranially. One minute later it was injected again with 0.5 c c of the spinal fluid. One minute later there was convulsion. Three minutes later there was passing of urine. Thirty-five minutes later the guinea-pig was still sick.

Another one of the guinea-pigs was injected with 0.5 c c spinal fluid from a case of dementia paralytica. One minute later there was a strong convulsion. Two minutes later the guinea-pig was biting on the floor. Twenty-five minutes later the guinea-pig was still sick, but had no convulsion.

A fifth guinea-pig was injected intracranially with 1 c c spinal fluid from a case of dementia paralytica. One minute later there was a convulsion. Two minutes later the guinea-pig was biting. One hour later the guinea-pig was still sick, but had no convulsion.

A normal guinea-pig, which was not injected with immune serum, was injected intracranially with 1 c c spinal fluid from a case of dementia paralytica. There was no reaction and the guinea-pig was not sick.

The passive anaphylaxis test with spinal fluid of dementia paralytica was investigated on the guinea-pig which was injected with an antispinal fluid (general paralysis) immune rabbit serum forty-eight hours previously. In one test of five cases we could find no reaction of the passive anaphylaxis with the injection of 1 c c spinal fluid from a case of dementia paralytica. In the other four cases we found a weak positive reaction of passive anaphylaxis with the intracranial injection of 1, 1.5, 0.5 and 1 c c spinal fluid from cases of dementia paralytica on the guinea-pigs, respectively, which were injected with 1 c c antispinal fluid (general paralysis) immune rabbit serum intraperitoneally after forty-eight hours.

DISCUSSION

It is evident from these experiments that two factors are concerned in the colloidal gold reaction. In fluids giving a curve there is present a precipitating substance, there may also be present a protective substance which modifies the action of this substance.

Globulin has commonly been regarded as the active constituent of the fluid giving the colloidal gold curve. It has also been suggested that albumin acts protectively, and that the different types of curves are due to varying ratios of the globulin and albumin.

A study of Table 18 shows that globulin usually gives a curve in Zone I, but may give a curve in Zone II. Table 19, giving the curves obtained from fluids not shaken (*a*) globulin in salt solution and (*b*) globulin in water, is interesting because of the fact that the curves tend toward Zone II. It is evident that globulin alone is capable of causing zonal reactions.

Albumin may give no precipitation of the colloidal gold, but in some instances it gives a well marked curve, usually in the second zone. While some of the curves from the albumin preparations were as

TABLE 25—PROTECTIVE ACTION OF GLOBULIN AND ALBUMIN

Color Change in Colloidal Gold Solution	C c of Globulin or Albumin Added to Gold Solution					
	0.03	0.02	0.01	0.005	0.0025	0.0012
Globulin	0	0	1	3	5	5
Albumin	0	1	3	5	5	

marked as those from globulin, it is apparent that albumin has less precipitating power, as a rule, than globulin.

Salt solutions have a precipitating action on colloidal gold. For study of the comparative protective power of globulin and albumin against these, solutions of equal strength of the two were used. It is evident from the tables relating to the protective action of albumin and globulin that globulin has a decided protective action, even more striking than that of albumin.

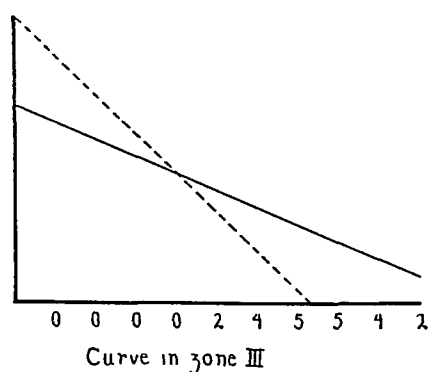
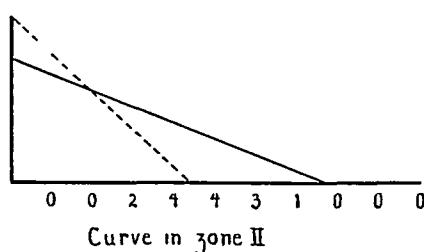
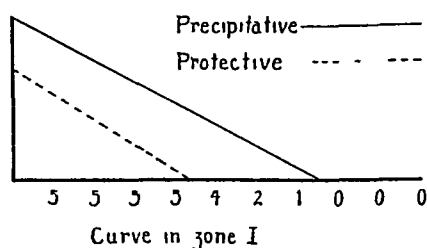
Table 25 shows the protective action of globulin and albumin from the same serum and used in equal amounts in salt solution.

From common knowledge alone of the albumin-globulin ratio in pathologic cerebrospinal fluids it does not seem likely that the curves are due primarily to the proportion of these substances. Kafka²⁴ finds the ratio in dementia paralytica to range from 7:3 to 5:1, in cerebrospinal syphilis, 12:1, and in meningitis it is most commonly 6:1. Further, the fact that curves are obtained from fluids giving a negative globulin test and, on the other hand, are not always present with fluids

²⁴ Kafka. Ueber den heutigen Stand der Liquor diagnostik, Munchen med. Wchnschr. 62:105, 1915.

giving a positive globulin reaction is suggestive that the albumin-globulin ratio is not the determining factor in the colloidal gold reaction

Table 18, giving various globulin ratios with reference to the colloidal gold curve, and Table 23, showing the albumin-globulin ratio, present a definite lack of parallelism between the total or proportional amounts of these substances and the colloidal gold curve



The fact that globulin has a definite protective action against salt solutions and that this power may be greater than that of albumin is further evidence that the albumin-globulin ratio, per se, is not the determining factor in the production of the curve

From these experiments it is evident that both albumin and globulin may exhibit precipitating and protecting action. The degrees of protection by the same globulin may be varied by changing the state of the globulin.

The ultrafiltration experiments showing a much greater decrease of the protecting than the precipitating substance in the ultrafiltrate would seem to indicate that the protective molecule is the larger. As to

what causes this alteration in the proteins, or whether it is due to the combination with some substance, such as lipoid, we have no evidence

Colloidal gold curves are dependent, therefore, on the ratio of the precipitating and protecting substances. Since our experiments show that these substances are present in varying amounts and that their precipitating and protective power decreases on dilution with varying degrees of rapidity, we may conclude that curves in Zones I, II and III are due to various combinations of these substances. If the precipitating substance markedly predominates over the protecting substance there results a curve in Zone I. If the protective power predominates over the precipitating power in the low dilutions, but rapidly diminishes with higher dilutions, a curve in Zone II is obtained. If both precipitating and protecting substances are present in considerable amounts, but the protective substance diminishes with dilution more rapidly than the precipitative substance, a meningitic type of curve is the result. The accompanying illustration gives a graphic representation of the three types of curves

CONCLUSIONS

- 1 Positive colloidal gold reactions are due to the presence of precipitating substances

- 2 Both precipitating and protecting substances are present in pathologic cerebrospinal fluid

- 3 Curves in Zones I, II and III are due to varying amounts and proportions of the precipitating and protecting substances

- 4 Albumin and globulin may possess both precipitating and protecting power

- 5 Ultrafiltrates of syphilitic and nonsyphilitic serums give curves that are more or less similar, but there tends to be a greater difference between the zones of reduction of the original and filtered serum in syphilitic than in normal cases

- 6 The protecting substance is decreased by ultrafiltration to a greater degree than the precipitating substance

- 7 Changes in the state of the protein modified precipitating and protecting powers

- 8 The salt solution used in the colloidal gold test partially neutralizes the protective action

AN EFFICIENT AND PRACTICAL METHOD FOR THE COUNTING OF RED BLOOD CELLS*

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Dreyer has quite recently described a method for the enumeration of blood cells and bacteria without the use of a counting chamber. His method simulates that first elaborated by Wright for the counting of bacteria in that it is dependent for its determination on a comparison of the relative number of corpuscles, which are of known titer per unit volume, and the elements to be counted. It differs principally, however, and has a much broader field of usefulness in that, instead of using normal erythrocytes and making smears for examination, a suspension of the red corpuscles of the hen carefully titered is used as a standard and this suspension mixed in known proportion with the elements, i.e. patient's erythrocytes, leukocytes, etc., to be counted allows for examination and comparative enumeration under the microscope. He points out the following distinct advantages: (1) it can be used with equal facility for counting erythrocytes, leukocytes and bacteria, (2) it does away with the use of a costly counting chamber, (3) it is quicker and less fatiguing to the eyes.

The method is to be commended for its universality and accuracy, however, it possesses certain disadvantages which greatly interfere with its practical clinical employment in enumerating erythrocytes. These are: (1) although the blood of the hen is obtainable it is not a common laboratory animal or readily secured in many hospitals, (2) the differentiation of the human and avian erythrocytes, while easy, is not instantaneous, (3) the method recommended for diluting the blood and then adding an equal volume of the suspension is an extra step over the hemocytometer method, (4) the use of a suspension standardized to contain about 20,000 corpuscles per cmm makes calculation of the patient's erythrocytes mathematically cumbersome. These disadvantages, though they in no way interfere with the accuracy of the method, do tend to limit it to a special laboratory technic and remove it from the sphere of clinical usefulness.

To overcome these disadvantages a procedure has been devised which has been found to be practical and efficient. Instead of avian erythrocytes, a suspension of crenated, fixed and stained human red blood cells is employed. This suspension is made up to contain 25,000 cells per cmm.

*From the Pathological Laboratories of the Royal Victoria Hospital and of McGill University.

*Aided by grant from the Cooper Fund.

Technic—The technic for enumeration requires (1) glass stoppered bottle containing the standard suspension, (2) pipets graded to deliver 1 c c and 0.005 c c¹, (3) test tube, plain glass slide, and cover slip

Preparation of the Standard Suspension—Fifty c c sterile 2 per cent sodium citrate in 0.85 per cent saline is placed in a sterile 300 c c Erlenmeyer flask. To this is added approximately 5 c c blood freshly drawn from a vein and free from clot. The blood should come from a person free from disease which alters the red blood cells, as anemia, etc., and may readily be obtained at the time of taking specimens for routine Wassermann examination. As the blood is added the mixture should be agitated slowly and the cotton wool plug then replaced in the mouth of the flask. The flask is kept at room temperature with gentle shaking up of the settled corpuscles daily or oftener to prevent their becoming too firmly precipitated and adherent at the bottom. At the end of three or four days, depending on the rate of evaporation, it will be noted that the color has changed from a bright to a slightly darker red, and if a drop is examined under the microscope, the cells will be found darker, smaller than when fresh and slightly crenated. Some show the alteration to a greater degree than others. There should be no clumping.

To the suspension, when the cells have attained this appearance, is added 200 c c Hayem's solution made up according to the following formula: Sodium chlorid, 1 gm, sodium sulphate, 5 gm, mercuric chlorid, 0.5 gm, distilled water, 200 c c. This must be filtered and perfectly clear. It should be borne in mind that all glassware employed throughout the process of preparing the suspension must be perfectly clean and rinsed in distilled water and all solutions free from insoluble dust particles, etc.

It is convenient if the suspension be now transferred to a tall, rather narrow glass stoppered bottle which will hold at least 500 c c or, better still, a 1,000 c c graduated glass stoppered cylinder. During the day the suspension is agitated and on the following day it will be found to have become light brown in color. The supernatant fluid is then siphoned off and replaced by fresh Hayem's solution. The cells are allowed to settle, the supernatant fluid is withdrawn and fresh solution is again added. The suspension is thus practically freed of the sodium citrate and the erythrocytes have become fixed. Under the microscope they appear small, crenated, brownish and quite highly refractile.

¹ Capillary pipets to measure 0.005 c c may be obtained from the Will Corporation, Rochester, N. Y., or the Topley Company, Ottawa, Ont.

The cells are now stained by adding 100 c c filtered eosin solution such as is employed for routine tissue staining or made up as follows Saturated solution of water soluble eosin, 10 c c , distilled water, 85 c c , saturated solution of picric acid, 5 c c , filter The mixture is shaken up well from time to time and the stain is allowed to act for twenty-four hours at the end of which time the supernatant fluid is siphoned off and replaced by Hayem's solution The excess of stain is thus removed and the process may be repeated if it is found after settling that the solution still contains much eosin

Titering the Suspension—Depending on the amount of blood originally obtained, the suspension is now diluted with Hayem's solution so as to contain approximately 25,000 cells per cmm Before counting it is best to transfer definite amounts, e g , 250 or 300 c c , to smaller glass stoppered bottles These are then brought to exact titer of 25,000 by making several careful counts with an accurate hemocytometer, fluid being added or withdrawn after settling as required

The suspension thus prepared is, so far as we have been able to judge, absolutely stable There should be no clumping which is inclined to occur if centrifugalization is employed The cells stand out clearly under the dry high power of the microscope as pink or red irregularly spherical masses about 5 microns in diameter

Technic for Adding Patient's Blood—The blood of which the erythrocyte count is to be determined is added to the standard suspension in the proportion of 1 to 200 This may be brought about in several ways with satisfactory results That procedure which is most convenient under the circumstances can be employed Where, as usually, it is desired not to withdraw a large amount of blood, the following procedure has been found very efficient

After thoroughly shaking the suspension, exactly 1 c c is measured into a test tube The tube should be perfectly clean but rinsing in distilled water without drying will not alter the result Dwarf test tubes measuring 10x1 cm are a convenient size The blood is obtained by finger or ear prick in the usual way and is allowed to run by capillarity or is sucked by means of rubber tubing and mouthpiece into a pipet graded to measure 0.005 c c The end is then wiped off on a piece of gauze and the contents discharged directly into the 1 c c of suspension in the test tube The pipet is washed clear by drawing up and blowing out the suspension several times The mixture is then shaken thoroughly and may be counted at once or the tube may be corked to prevent evaporation and consequent crenation of the blood disks and set aside to be examined any time when convenient within twenty-four hours

Another method consists in the use of the regular erythrocyte pipet provided with hemocytometers One with a relatively large bore

so that the contents may be expelled readily is preferable. The pipet is filled with patient's blood to the 0.5 mark and then diluted with suspension to 101. It is best to remove a small quantity of the suspension from the large bottle for this purpose. The pipet is then shaken, and after discharging the first three or four drops, the balance is expelled into a clean test tube and either counted or corked and set aside, as stated above. It is obvious that there is a slight fallacy here as the mixture is minus a quantity of suspension equal to the amount of blood employed, namely $\frac{1}{200}$ part. For practical purposes, however, this can be disregarded as it alters the count of corpuscles per cubic millimeter by only a similar proportion and this is of no clinical consequence.

When a large quantity of blood is withdrawn by venous puncture, as in connection with chemical metabolic blood calculations, and the fluid preserved free from clot by the use of a few crystals of potassium oxalate, a larger quantity of blood may be conveniently employed. It is only necessary to keep in mind to use a relatively larger amount of suspension, so that the proportion of 1:200 may be preserved, as for example 0.05 c. c. blood to 10 c. c. suspension.

Counting the Erythrocytes—The erythrocytes may be counted any time within twenty-four hours, provided the suspension has been properly freed of a large amount of uncombined eosin and care is taken by corking to avoid crenation of the cells. This possibility is of considerable practical importance, as, for example, in ward work where several specimens may be taken at one time and removed to the laboratory, or in private practice when examining blood of persons outside the hospital or office.

When ready to proceed, the mixture should be shaken thoroughly. This is quickly accomplished by removing the cork and placing the thumb over the orifice of the tube. A medium sized drop of the mixture is now transferred to a clean glass slide and covered by a cover slip. Bubbles should be avoided. It will then be found that the cells settle almost instantaneously into quiet position. The cells are now examined under the high dry power of the microscope. Reduced light facilitates differentiation, and the pale biconcave circular disks of the patient stand out in distinct contrast to the red crenated corpuscles of the standard suspension.

Considering the technic employed, it is obvious that if the blood which is being examined has a normal erythrocyte count, that is between 4,500,000 and 5,000,000 cells per c. mm. the corpuscles and standard suspension cells in the mixture will be in the proportion of approximately 1 to 1 and will appear in practically equal numbers in the microscopic field. Thus, almost at a glance and without counting one may obtain this information and draw immediate conclusion as regards a normality or deficiency in red blood cells.

For enumeration it is necessary to count and record the exact number of each type of cell in several fields. The total number of cells in a field may be altered by the size of the drop which has been placed on the slide and the size of the cover slip employed. Furthermore counting may be facilitated, as Dreyer suggests,² by inserting on the metal diaphragm within the eyepiece a small circle cut from light cardboard in the center of which a square aperture has been made. After a little practice 100 cells per field may be counted rapidly and accurately.

The number of fields examined and the total number of cells counted can be modified by the degree of accuracy which it is desired to attain. If the cells have been mixed properly by shaking, the proportion will be found to vary but slightly in different fields, especially if the total number of cells per field is high. For accurate enumeration it is advisable that a total of 1,000 cells be counted from each of two drops examined.

Calculation of the Patient's Erythrocyte Count—The total number of each type of cell is now computed and by multiplying the sum of the fresh corpuscles by 5,000,000 and dividing by the sum of the standard suspension cells, the number of patient's red blood corpuscles per cubic millimeter is quickly determined. As a matter of fact, the six ciphers may be disregarded and simply "5" used, care being exercised to preserve the decimal.

For example. Suppose the sum of standard suspension cells in several fields to be 625, and the sum of the patient's corpuscles in the same fields 456. Then

$$\begin{array}{r} 625 \quad 456 \quad 5 \quad X \\ \quad \quad 456 \times 5 \\ X = \frac{\quad}{625} \text{ or } 3\,648 \end{array}$$

$$\text{Erythrocyte count} = 3,648,000$$

Unless a very large number of cells is counted, it of course, adds nothing to the accuracy to carry the decimal beyond three figures.

CONCLUSIONS

Employing the same principle of comparing the elements to be counted with those of a titered standard suspension, as in Dreyer's method, a procedure is devised which has distinct advantages for the enumeration of erythrocytes and offers a method which is rapid, accurate and clinically practicable.

I am indebted to the metabolism department of the hospital and to Dr McIntyre particularly for obtaining blood for the work.

² Dreyer, Georges. A Simple Procedure for the Accurate Enumeration of Blood Cells and Bacteria Without the Use of a Counting Chamber, *Lancet* **1** 219 (Jan 29) 1921. The Counting of Blood Cells and Bacteria, *J A M A* **77** 1166 (Oct 8) 1921.

THE MECHANISM OF HAY-FEVER *

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The mechanism of hay-fever is worthy of careful study for the reason that hay-fever is quite typical of the great group of clinical conditions presumably due to a natural sensitiveness to some foreign substance. This sensitiveness is termed allergy. Up to the present time at least, allergy has been recognized only in man. A tendency to it is often inherited. It manifests itself by different symptom complexes each quite characteristic whenever the individual comes in contact with the specific foreign substance.

When this contact is by way of the respiratory tract, the symptoms are usually referable to disturbances in the nose and the patient is said to have hay-fever. This hay-fever may be either seasonal or perennial. Seasonal hay-fever would appear to be a very clear cut disease with a definite and well defined etiology, because the symptoms begin and end at the exact time when the particular pollen appears and disappears in quantity in the atmosphere, also because various biologic reactions to the pollen are manifested by hay-fever patients which are not manifested by normal people, and, finally, because treatment with an extract of the pollen brings about relief from symptoms in the majority of patients.

In New England there are at least two important types of seasonal hay-fever, namely (1) early hay-fever, which begins in early June and lasts until the middle of July and is due to a sensitiveness to the pollen of the common grasses, and (2) late hay-fever, which occurs from the middle of August until the first frost and is due to a sensitiveness to the pollen of ragweed, or rarely the pollen of goldenrod. The studies here reported have been made on patients with late hay-fever who were sensitive to ragweed.

As regards the mechanism of hay-fever, there are several possible explanations. First, that it is quite the same as the mechanism in the artificial sensitization of animals and man, namely, that it depends on the interaction of antigens and antibodies. We know that a rabbit or a guinea-pig actively sensitized to horse serum, as well as a man recovered from the serum disease following a dose of diphtheria antitoxin from a horse, will give an immediate local reaction when a drop of diluted horse serum is applied to the skin. And in hay-fever, it is well known that when an extract of the specific pollen is applied to the skin or to the mucous membranes of the patient, an immediate local reaction takes place.

* From the Medical Services of the Massachusetts General Hospital

Since there is no pathologic study of the skin test in the literature, we can only assume that it is the cells of the skin which are the seat of the reaction. We know that urticarial wheals are characterized by a transudation of serum when spasm of the skin capillaries is followed by dilatation and effusion. It is this effusion which by displacing the blood causes the central pallor of the wheal. This would indicate that the primary disturbance is in the cells of the blood vessels rather than in the cells of the skin, and that as suggested by Neisser¹ the condition is due to a vasomotor affection of the nerves supplying these blood vessels.

To explain such a local reaction as well as the local symptoms of hay-fever there are several possibilities

1—The cells of the patient may contain antibodies not present in the cells of normal persons but which are added to the normal cell function. Perhaps, the best evidence of this addition of cellular antibodies is the fact that when an antigen is applied repeatedly to the same spot on the skin of a hypersensitive patient, the local reactions following each application become progressively less—indicating a local exhaustion of these antibodies.² This same exhaustion occurs in the entire skin and mucous membranes but in much less marked degree as a result of the successful treatment of hay-fever.

2—The cells of hay-fever patients may lack something which is present in normal cells so that in the former there is a failure to neutralize some reaction producing element in the antigen. An analogy is found in those cases in which a positive Schick test indicates an absence of normal diphtheria antitoxin. Incidentally, the failure to demonstrate precipitins might imply a true toxin-antitoxin reaction. The suggestion that ragweed acted as a true toxin was made in 1905 by Dunbar.³ However, the symptoms following an overdose of ragweed are not those following an overdose of a toxin, and, furthermore, it has been shown⁴ that the blood serum of normal persons and of those hay-fever patients who are improved by pollen treatment is not capable of so neutralizing even a very dilute pollen solution that it will fail to give a skin test in another susceptible patient. Also, so far as treatment is concerned, the dried blood serum of a normal horse is about as effective as is Dunbar's "Pollantin"—which is the dried blood serum of a horse treated with pollen.

3—There may be some substance present in the circulating blood of the patient which either reacts with the antigen to make it toxic or which in some way facilitates the contact between antigen and cell

1 Neisser, A. Quoted by Bruck in his *Experimentelle Beiträge zur Ätiologie und pathogenese der Urticaria* Arch f Dermat u Syph **96** 241, 1909

2 Mackenzie, G. M., and Baldwin, L. B. Local Desensitization in Hypersensitive Individuals and Its Bearing on the Prevention of Hay-Fever, Arch Int Med **28** 722 (Dec.) 1921

3 Dunbar, W. P. Hay-Fever Berl klin Wchnschr, No 26, p 797, 1905

4 Rackemann, F. M. The Specific Treatment of Hay-Fever, Boston M & S J **182** 295, 1920

contents If such substance exists in the blood, it should be demonstrable whenever the skin test is positive We know that in serum disease circulating antibodies and skin tests do develop and appear together, but, on the other hand, whereas circulating antibodies disappear quite promptly in a few weeks, or less, the positive skin test will remain demonstrable often for years, so that it would be difficult to imagine any close dependence between them

Circulating antibodies play a definite and important rôle in experimental anaphylaxis The serum of a sensitized animal can cause a precipitate when in contact with the specific serum The detection of circulating antibodies in hay-fever is at best difficult and inconstant Koessler⁵ claims to have transferred pollen sensitiveness from a patient to guinea-pigs by means of the blood serum, and Clowes⁶ demonstrated specific precipitins in a few cases before the onset of the hay-fever season, but not in all cases However, Cooke, Flood and Coca,⁷ in a series of carefully conducted experiments, were not able to demonstrate circulating antibodies by which the sensitiveness to ragweed could be transferred passively from man to animals, and the author has failed to find precipitins in the blood serum of hay-fever patients in spite of repeated attempts made in various stages of the disease and during treatment

These precipitin tests were made by adding together 0.5 c.c. of the patient's serum never more than twenty-four hours old and used unheated, and 0.5 c.c. of ragweed solutions diluted in series from 1:500 to 1:500,000

These dilutions were each made from an original stock solution made by extracting 10 gm. of pure ragweed pollen in 100 c.c. of saline solution which contained 0.5 per cent phenol and two hundredth normal sodium hydrate

Readings were made not only after an incubation for one hour at 37° C, but again after the tubes had been kept in the icebox over night In spite of many trials, no precipitates were observed

Largely because of this difficulty of demonstrating any circulating antibodies, the question has arisen as to whether ragweed pollen can act as an antigen or not Parker⁸ has recently found that by injecting enormous doses of ragweed pollen extract intraperitoneally to guinea-pigs over long periods of time, she can sensitize them so that the uterus suspended in Ringer's solution will give a well marked contraction when ragweed extract is added to the bath Thus it seems demonstrated that plant pollens are or may be weakly antigenic

5 Koessler, K. K. The Specific Treatment of Hay-Fever, Forchheimer's Therapeutics of Internal Diseases 5:671

6 Clowes, G. H. A. Certain Specific Reactions Exhibited by Hay-Fever Cases, Proc. Soc. Exper. Biol. & Med. 10:69, 1913

7 Cook, R. A., Flood, E. P., and Coca, A. F. Hay-Fever, the Nature of the Process and of the Mechanism of the Alleviating Effect of Specific Treatment J. Immunol. 11:217, 1917

8 Parker, Julia, T. The Antigenic Properties of Ragweed Pollen, Proc. Soc. Exp. Biol. & Med. 18:237, 1921

Hence, of the three possible explanations of the positive skin test in hay-fever, we may conclude that the theory of additional antibodies peculiar to the condition and not found in normal individuals is the most satisfactory

It must be noted, however, that the presence of these antibodies by no means precludes the possibility that circulating antibodies are also important, although, as in serum disease, each appears—as judged by our crude methods of demonstration—to be independent of the other

As regards the relation between hay-fever and experimental anaphylaxis, one other point needs emphasis It is characteristic of anaphylaxis that an animal which has recovered from the reaction following the parenteral injection of a second nonlethal dose of the specific protein will be refractory to a third dose of that protein Such a desensitization in hay-fever and allergy is by no means so sure, for

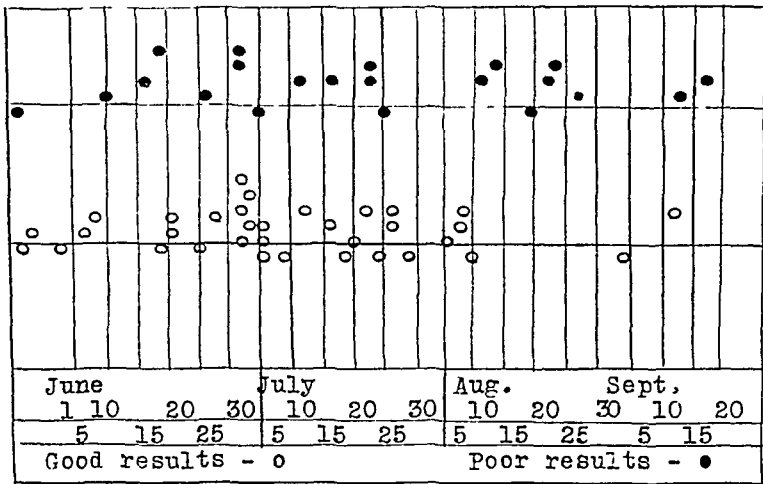


Chart 1—Relation of the end results to date of first dose

as previously shown,⁴ patients with late hay-fever who have reacted with urticaria and asthma to an overdose of pollen extract on one day, will on the next day show a similar reaction to the same dose of the same pollen extract

Since the demonstration of circulating antibodies is so difficult and irregular, we have at present only two satisfactory methods of study First, the relation of the end results to the technic of treatment, and second, the changes in the skin test following treatment As regards the technic of treatment in hay-fever Aside from the choice of a particular pollen extract, there may be at least three factors variable for each patient

Chart 1 demonstrates that good results as well as poor results may follow without regard to the date on which the series of preventive inoculations is begun

Chart 2 shows quite clearly that both good and bad results may follow either a large or small number of treatments as well as a large or small total dosage during the season. Such findings are to be explained by the variation in the degree of sensitiveness of the individual patient.

If we assume that hay-fever is dependent on an excess of fixed cellular antibodies, it is easy to understand that the degree of sensitiveness can be determined by the highest dilution of pollen extract which is capable of producing a skin test⁹. When patients are extremely sensitive, that is when they have a large excess of cellular antibodies and when consequently they react positively to very high

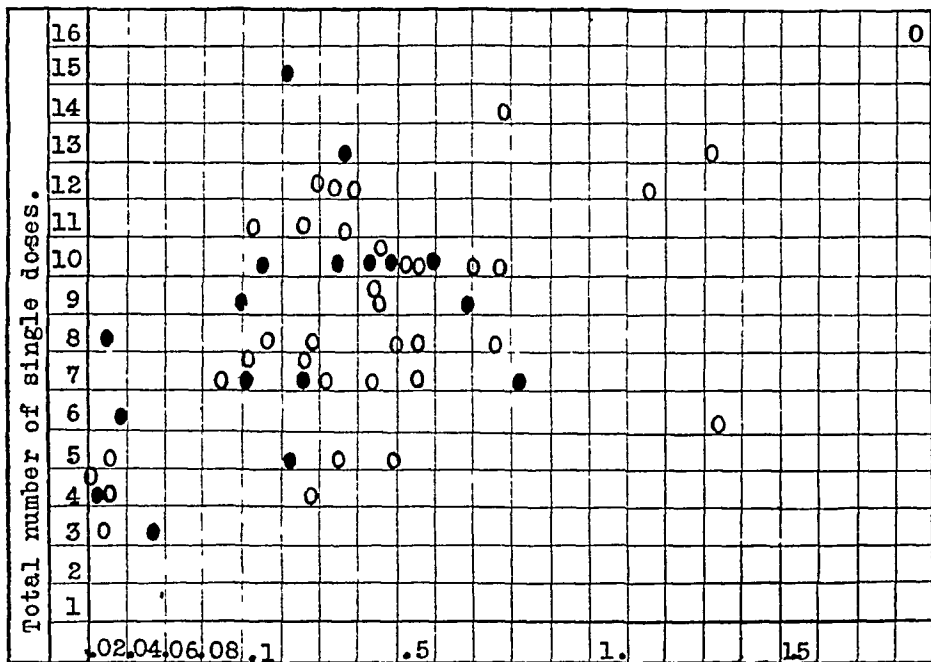


Chart 2—Relation of end results to number of doses and to total dosage of pollen extract. The total dosage is expressed in cubic centimeters of 1:100 dilution. Good results are shown by the circles, the poor results by the dots.

by relatively small doses of extract which would suffice to reduce the dilutions of ragweed extract, they theoretically ought to be benefited great excess of these cellular antibodies.

In practice, this theory does not hold. However, it is dangerous to make any very definite statement because individual patients vary so widely in their reactions to treatment even if, at the first visit, their skin tests seem quite the same. For example, A group of at least eight patients suffering from late hay-fever, on the first visit gave a skin test to a 1:10,000 dilution of ragweed pollen extract. Of these, four were improved by treatment and each of the four had a total dose

⁹ Walker, I. C. Sensitization and Treatment of Bronchial Asthmatics with Pollens, *Am J M Sc* **157** 409, 1919.

of more than 0.6 cc of the 1:100 dilution. Two patients were not improved and each received less than one-third of the above mentioned dose.

A group of at least twenty-four patients gave a skin test to dilutions of ragweed no higher than 1:1,000. Sixteen of them were improved by treatment, eight were not improved, and yet the amount of treatment given was about the same in each group. Hence, there is apparently only a very rough relation between the original skin test and the results of treatment with a given dosage.

The degree of sensitiveness does seem to diminish when the treatment is successful. Skin tests performed in September in successfully treated cases of late hay-fever show reactions which are ordinarily of somewhat less size than similar tests done in May. The reduction is, however, rarely more than ten times, that is, if in May they reacted to a 1:5,000 dilution, in September they will still react to a 1:500 dilution. I have never seen a skin test to ragweed disappear entirely even in cases in which the treatment was entirely successful. Observations of this kind are quite difficult of accurate interpretation for the reason that ragweed extracts do not hold their potency indefinitely and such observations must be made with freshly made extracts using exactly the same sample of pollen.

Since, however, the skin test does seem to diminish even in small degree, this fact alone would tend to substantiate the theory that hay-fever is due to an excess of fixed cellular antibodies. The apparent absence of circulating antibodies may be due to our crude method of their demonstration.

In order to demonstrate that fixed antibodies were attached to other cells than those of the skin of hay-fever patients, I had hoped to obtain a vermiform appendix or other specimen of smooth muscle of such a patient which could be tested for specific cellular sensitiveness by Dale's method¹⁰ but so far no specimen has been found. The red blood corpuscles of hay-fever patients might show a reaction to pollen extracts different from the corpuscles of normal persons. In this connection, it is of interest to recall some observations made in 1916 during the course of other experiments on serum disease. At that time one problem was to determine whether the red blood corpuscles of a patient injected with foreign serum (horse serum) showed any change in their reactions to the serum before and after the injection. The study was made on the red blood corpuscles of patients with pneumonia. Each patient had received fairly large doses of antipneumococcus horse serum intravenously. In no case was there any change observed in the mixtures of horse serum and cells before and after this specific treatment, in spite

¹⁰ Dale, H. H. The Anaphylactic Reaction of Plain Muscle in the Guinea-Pig. *J. Pharmacol. & Exper. Therap.* 4: 167, 1913.

of the fact that in most of the cases positive skin tests and precipitins had developed at the time when the second specimen of cells was obtained

The effect of the active sensitization of guinea-pigs to horse serum on the red blood corpuscles of these guinea-pigs was also studied and again it was found that there was no difference in the reaction of guinea-pig cells to horse serum before and after sensitization. Horse serum has always a very variable effect on guinea-pig corpuscles, but the variations in a control series of guinea-pigs which were bled at the same intervals showed irregularities and changes no greater or less than those occurring in the sensitized animals

Further experiments planned to determine whether the cells of sensitized guinea-pigs are hemolyzed by the corresponding antigenic serum in the presence of complement were entirely negative

In order to study the reactions of the red blood corpuscles in hay-fever patients, blood cells were obtained from a considerable number of patients with late hay-fever—each of whom gave a well marked skin test to ragweed pollen extract at the time of bleeding

The tests were always set up on the day of the bleeding. Blood from the arm vein was added in small quantities to a test tube full of salt solution, mixed thoroughly, and the cells were then washed three times with saline being finally made up in a 5 per cent suspension in saline solution

For the test equal quantities (0.5 cc) of cell suspension and ragweed extract 1:100 were mixed together and incubated at 37°C for one hour in the water bath

In no case was hemolysis observed, in spite of the fact that specimens of cells were taken from patients during various stages of hay-fever and from other patients after the hay-fever season

When the same test mixtures were held over night in the icebox, there were no changes noted which were different from the controls—that is, from mixtures containing red corpuscles of normal persons and ragweed extract. That this absence of hemolysis was not due to the absence of complement is shown by the fact that when the fresh unheated serum of the patient was added to the test mixture of ragweed extract and the same patients' cells, there still was no hemolysis

Thus, if we can judge of the presence of antibodies in red blood corpuscles by whether or not hemolysis occurs in the presence of the antigen, we may say that no such specific antibodies were demonstrated in the red blood corpuscles of hay-fever patients, a statement which is in entire accord with the findings already noted in typical anaphylaxis and in serum disease

DISCUSSION

Hay-fever is a typical example of the many varieties of natural sensitiveness. The mechanism of hay-fever depends on the fact that the cells contain specific antibodies which are not present in the cells

of normal persons That the symptoms are not due to a lack of function which is normally present is indicated by the absence of any antitoxin in the blood, such as occurs with a positive Schick test in diphtheria

That the symptoms are not due to circulating antibodies which have a constant action either on the antigen or on the cells is shown not only by the inability to demonstrate such antibodies in the blood but is indicated also by the analogy in serum disease where the establishment of fixed cellular antibodies, as demonstrated by the skin test, is later uninfluenced by the disappearance of circulating antibodies

The great variations in the results of specific treatment by a given technic are readily explained by the variations in the degree of sensitiveness, although it is evident that the delicacy of the skin test is only a crude measure of the number of cellular antibodies Finally, all attempts to demonstrate antibodies fixed to the red blood corpuscles of the patient by adding antigen to these corpuscles have failed

It seems worth while to call attention to the close relation between the mechanism of allergy and of immunity Specific antibodies are present in both conditions In allergy, these antibodies are predominantly fixed in the cells, in immunity, the antibodies are predominately in the circulating blood However, in neither condition are the antibodies in one location exclusively In allergy the symptoms probably depend on reactions which take place in the cells That no such symptoms occur in immunity is shown by the experiments of Manwaring and Kusama¹¹ Reactions following perfusion with serum mixtures were obtained with the lungs of immune guinea-pigs—which reactions were entirely analogous to those obtained with the lungs of anaphylactic guinea-pigs The fact that, in life, immune guinea-pigs show no reaction to injections of the specific antigen, although it is clear that their cells do contain fixed antibodies, must be explained by the protection afforded by the excess of circulating antibodies The difference between allergy and immunity, therefore, depends on whether antibodies are predominant in the cells or in the blood

11 Manwaring, W H, and Kusama, Y Analysis of the Anaphylactic and Immune Reactions by Means of the Isolated Guinea-Pig's Lungs, *J Immunol* 2 157, 1917

FACTORS IN LEUKOCYTOSIS *

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INTRODUCTION

Injection of a foreign protein into the animal body leads to certain well defined phenomena which should be familar to all. If sensitization, following a previous dose, be present, anaphylactic shock may result. Otherwise one expects, first, a latent period with no outward manifestation but during which it is believed that the protein is undergoing chemical change into less complex and more stable substances, and, second, a rise of temperature with an increase of the neutrophil polymorphonuclear white cells of the blood. If the injection be subcutaneous or intramuscular, the sequels are mild and last over a day or more, if the injection is intravenous, they are relatively violent and subside in a few hours. Vaughan¹ has considered the excess heat production as being due to three factors, (1) the unusual activity of the cells supplying the proteolytic enzyme, (2) cleavage of the foreign protein, (3) the destructive reaction between the split products of the foreign protein and the proteins of the body. Fever may also be produced by the rapid withdrawal of the major portion of the available water of the body. This method of investigation was first systematically exploited by Balcar, Sansum and Woodyatt² and is best carried out by the intravenous injection of hypertonic salt solution. This, in turn, produces a diuresis which, in the course of a few hours, may cause the fluid output to exceed the intake by many hundred cubic centimeters.

It has been pointed out in a previous communication³ that acute water shortage results in an increased rate of protein metabolism with a rapid increase in the formation of the endproducts which quickly pile up in the blood. In this case but one of the sources of fever mentioned by Vaughan can be a factor, namely, chemical heat from the changes in the body protein. These changes resemble, to a striking degree, certain features of many of the acute bacterial infections,

* From the Buhl Memorial Laboratory, Harper Hospital

1 Vaughan, V C, Vaughan, V C, Jr, and Vaughan, J W. Protein Split Products in Relation to Immunity and Disease, 1913. Lea & Febiger, Philadelphia pp 373-416

2 Balcar, J O, Sansum, W D, and Woodyatt, R T. Fever and the Water Reserve of the Body, Arch Int Med **24** 116 (July) 1919

3 Bacon D K, Anslow, R E and Eppler, H H. Intestinal Obstruction, Arch Surg **3** 641 (Nov) 1921

notably colon bacillus peritonitis, pneumonia and the acute pyogenic infections, and will be more fully discussed at a later time. The present investigation was undertaken to determine whether fever due to the increased protein metabolism of acute water shortage was accompanied by a leukocytosis similar to that seen after the injection of a foreign protein, and if so to consider its bearing on the subject of leukocytosis in general.

METHODS

Dogs were used for experiment and were all, so far as could be determined, in good health at the time. Dehydration was produced by injection into the femoral vein of a solution consisting of sodium chlorid, 99 gm, potassium chlorid, 3.3 gm, calcium chlorid, 2.86 gm, water, 2,000 c c. This represents the concentration of Ringer's solution multiplied by 5.5. Sodium chlorid alone was avoided because of the sodium poisoning said to occur when it is used on tissues in high concentration and unaccompanied by the physiologic antagonists—potassium and calcium. This solution will, later, be referred to as dehydration fluid. It was given through a graduated funnel such as is used in the administration of arsphenamin. This was connected by a rubber tube to a small glass cannula which could be tied into the vein. The rate of flow was easily controlled by a small screw clamp on the tubing. Solution, glassware and tubing were, of course, kept strictly aseptic.

In general, no attempt has been made to give the solution at a fixed rate, but the calculated amount is allowed to run in quite rapidly, thus 500 c c could be given in from fifteen to twenty minutes. It was found that if enough solution were given to leave a high residual salt concentration in the body after exhaustion of the available water and death took place in less than six hours the changes under investigation, while they occurred in some measure, were abortive and ill defined. Thus the effort has been to so regulate the amount injected that a smaller residual salt content was left and that death came in from twelve to twenty-four hours. This permits of ample time for the interesting features to unfold and develop. Success, within these limits, has been secured, in a majority of experiments, by administration of 50 c c of the dehydration fluid per kilo of body weight of the animal. The process is somewhat influenced by surroundings, and it, more particularly the rise of temperature, may be accelerated by placing the animal in a warm room or held in check by placing it in a cool room. In the latter case there may be a marked difference between rectal temperature and that of the internal organs. The increased urinary output following the injection was collected through a retention catheter and allowed to drip into a graduate where the amount could be read at any time. Venesection was done under 1 per cent procain anesthesia. All experimental animals were kept under morphin as a sedative.

EXPERIMENTAL DATA

Information on eight dogs is given in Tables 1 to 8. In Dog 1 figures for the concentration of total noncoagulable blood nitrogen are given at the same intervals as elapsed between temperature readings.

EXPLRIMENT 1—Dog 1, female, weight 13,440 gm, was injected with 39 c c per kilo of dehydration fluid.

TABLE 1—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 1

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leukocytes	Poly-morpho-nuclears, per Cent	Small Lympho-cytes, per Cent	Mono-nu-clears, per Cent	Eosino-phils, per Cent
6 30 p m	101.6	0	0	22.2	1,400	81	10	9	0
7 30 p m	103.2	525	1,000	25	3,600	78	42	0	0
8 30 p m	101.0	525	1,200	28.6	5,800	82	12	6	0
10 30 p m	103.6	525	1,400	30.0	11,000	89	6	5	0
12 30 a m	102.8	525	1,570	34	12,800	92	3	5	0
9 30 a m	105.8	525	1,500	60.0	17,300	93	2	5	0

EXPLRIMENT 2—Dog 3, female, wt 10,900 gm, was injected with 60 c c per kilo of dehydration fluid.

TABLE 2—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 3

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leukocytes	Poly-morpho-nuclears, per Cent	Small Lympho-cytes, per Cent	Mono-nu-clears, per Cent	Eosino-phils, per Cent
8 55 p m	100.6	0	0	27.3	11,500	86	8	6	0
10 00 p m	99.4	550	730		8,000	75	22	3	0
12 00 m	102.2	550	1,120		15,600	91	6	3	0
6 00 a m	106.2	550	1,270	60	10,200	92	4	4	0

EXPERIMENT 3—Dog 4, female, wt 5,920 gm, was injected with 45 c c per kilo of dehydration fluid.

TABLE 3—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 4

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leukocytes	Poly-morpho-nuclears, per Cent	Small Lympho-cytes, per Cent	Mono-nu-clears, per Cent	Eosino-phils, per Cent
9 45 p m	100.4	0	0	37.5	8,400	74	14	11	1
10 45 p m	100.2	265	360		5,000	63	30	7	0
12 00 m	100.4	265	510		11,600	80	15	4	1
7 00 a m	101.0	265	640		16,400	85	8	7	0
11 00 a m	99.2	265	650		21,600	88	8	4	0
3 00 p m	100.0	265	660		15,900	89	6	5	0
7 00 p m	100.6	265	665		15,700	89	5	6	0
11 00 p m	101.4	265	670	67					

and blood counts to illustrate the growing velocity of protein catabolism and the parallel rise of the white count. Additional data on protein disintegration in acute water shortage as a process of increasing momentum have already been published.³

It must be realized that the withdrawal of repeated samples of blood from a small animal constitutes, in itself, an appreciable hemorrhage. As hemorrhage is a recognized cause of leukocytosis a possible source of error was apparent and in other animals only normal and

EXPERIMENT 4—Dog 5, female, wt 13,210 gm, was injected with 50 c c per kilo of dehydration fluid

TABLE 4—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 5

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leuko cytes	Poly-morpho nuclears, per Cent	Small Lympho cytes, per Cent	Mono nu clears, per Cent	Eosino phils, per Cent
9 50 p m	99.8	0	0	18	6,200	75	18	6	1
11 00 p m	100.6	650	640		5,900	70	24	6	0
1 00 a m	101.4	650	990		9,600	82	10	8	0
9 00 a m	98.6	650	1,170		12,300	89	6	5	0
4 00 p m	99.8	650	1,175		17,300	94	2	4	0
7 00 p m	102.6	650	1,180	52	21,200	94	1	5	0

EXPERIMENT 5—Dog 8, male, wt 11,710 gm, was injected with 45 c c per kilo of dehydration fluid to which was added 2 per cent HCl

TABLE 5—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 8

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leuko cytes	Poly-morpho nuclears, per Cent	Small Lympho cytes, per Cent	Mono nu clears, per Cent	Eosino phils, per Cent
10 00 p m	100.8	0	0	20	4,300	79	11	10	0
11 30 p m	99.0	530	440		4,600	63	28	4	0
12 30 a m	100.0	530	640		7,300	73	21	6	0
1 30 a m	101.8	530	730		9,900	81	14	5	0
2 30 a m	103.0	530	780		14,900	86	10	4	0
3 30 a m	104.4	530	800		19,200	91	7	2	0
4 30 a m	105.2	530	810		19,300	91	6	3	0
7 00 a m	106.2	530	815	50	21,500	90	6	4	0
	Liver								

EXPERIMENT 6—Dog 10, male, wt 8,660 gm, was injected with 50 c c per kilo of dehydration fluid

TABLE 6—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 10

Time	Temperature	Fluid Intake C c	Fluid Output C c	Blood Nitrogen, Mg	Total Leuko cytes	Poly-morpho nuclears, per Cent	Small Lympho cytes, per Cent	Mono nu clears, per Cent	Eosino-phils, per Cent
5 45 p m	101.2	0	0	24	6,400	75	6	18	1
6 45 p m	100.0	435	420		5,400	72	20	8	0
7 45 p m	99.6	435	630		10,600	83	9	8	0
8 45 p m	100.2	435	760		11,800	86	6	8	0
10 45 p m	101.2	435	900		13,700	92	4	4	0
12 45 a m	101.6	435	980		18,700	91	3	6	0
7 45 a m	100.2	435	1,005		17,600	92	2	6	0
12 00 m	98.6	435	1,010		22,400	94	0	6	0
6 30 p m	106.6	435	1,020	67					
	Liver								

terminal specimens were taken for blood nitrogen estimation, about 8 or 10 c c in all, the intermediate values being left to the imagination of the reader. Blood counts were made from small drops obtained by pricking the ears. Temperature readings were made per rectum unless

otherwise stated Blood nitrogen is given in milligrams per hundred c c , leukocyte counts in thousands per cubic millimeter Large lymphocytes and transitionals were counted together as mononuclears Fluid intake and output are given as cumulative quantities

These eight experiments show certain features in common and they will be pointed out here to be commented on later About one hour after the injection is completed a slight leukopenia exists It is not marked and the count may be found essentially the same It is, however, associated with a drop in the polymorphonuclear count and an increase of the small lymphocytes So marked is this lymphocytosis

EXPERIMENT 7—Dog 6, male, wt 8,010 gm, was injected with 50 c c per kilo of dehydration fluid

TABLE 7—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 6

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leuko-cytes	Poly-morpho-nuclears, per Cent	Small Lympho-cytes, per Cent	Mono-nu-clears, per Cent	Fosino-phils, per Cent
9 45 p m	100.6	0	0	30	6,000	80	6	14	0
11 00 p m	100.6	405	475		5,100	71	24	5	0
12 00 p m	99.6	405	550		12,200	87	3	10	0
7 30 a m	98.2	405	705		21,800	90	4	6	0
10 00 a m	103.0	405	710	86	23,200	93	2	5	0

EXPERIMENT 8—Dog 9, male, wt 8,140 gm, was injected with 30 c c per kilo of dehydration fluid which was followed very slowly with 15 c c per kilo of 5 per cent sodium bicarbonate solution

TABLE 8—SEQUELS OF ACUTE WATER SHORTAGE IN DOG 9

Time	Temperature	Fluid Intake, C c	Fluid Output, C c	Blood Nitrogen, Mg	Total Leuko-cytes	Poly-morpho-nuclears, per Cent	Small Lympho-cytes, per Cent	Mono-nu-clears, per Cent	Fosino-phils, per Cent
9 30 p m	100.0	0	0	40	7,000	79	6	14	1
10 30 p m	98.0	345	480		6,500	78	13	9	0
11 30 p m	96.0	385	650		12,000	87	7	2	4
12 30 a m	96.2	385	700		13,500	89	3	6	2
8 30 a m	101.4	385	780		24,600	89	3	8	0
2 30 p m	101.8	385	790		26,400	93	1	6	0
6 30 p m	102.2	385	795		27,500	92	5	3	0
10 00 p m	105.4	385	795	67	27,600	93	2	5	0

that it suggests more than a merely relative increase and resembles an actual addition of these cells to the circulating blood By the same token a dilution phenomenon as a cause of the leukopenia is rendered improbable Following this early leukopenia there is a steady increase of the total white cell count to levels far above normal This increase is apparently almost wholly confined to the neutrophil polymorphonuclear cells and there is a marked relative decrease of the remaining types, which decrease seems most constant and uniform in the small lymphocytes In Dog 3 the high initial count of 11,500 was accompanied by a full stomach and upper intestine and was, we presume, a digestive

leukocytosis The fall in the final counts in Dogs 3 and 4 we are unable to explain on any basis except that of the early formation of antemortem white blood cell clots and immobilization of many of the circulating leukocytes Both dogs showed, at necropsy, intracardiac white clots

There is a parallel rise of the nonprotein nitrogen of the blood indicating progressive catabolism of protein and lastly there are wide variations in the body temperature If the experiment be quickly concluded the temperature may progressively rise in response to quite violent protein disruption If a longer period elapse between start and finish the initial trend of the temperature may be downward and a recovery and rise above normal be apparent only in the last third or quarter of the time Indeed, the outer surface and orifices of the body may show no elevation of temperature at any time, and it may be found only on examination of the deep structures, as in Dog 10 As body temperature is a balance between heat formation and elimination, it involves too lengthy a discussion for this place Suffice it to say that the discrepancies noted indicate faulty distribution, unequal formation in different areas and other phenomena dependent on a failing circulation and a lack of water with its buffer action in heat absorption and transportation

In dogs 8 and 9 the effects of an increasing acidosis and of increasing the alkali reserve were respectively tried in combination with dehydration If one case of each be of value, the acid-base balance of the body exerts no very important influence on either leukocyte count or blood nitrogen increase

Other experimental animals showed changes similar to those reviewed above In control animals injected with 50 c c of Ringer's solution per kilo of body weight no variations were noted in temperature, blood nitrogen or white cell count which exceeded the limits of normal A mild upward trend might be observed in animals kept for twenty-four hours, particularly if placed in a warm room

COMMENT

It has been noted heretofore that injection of a foreign protein gives rise to a leukocytosis only after the lapse of an interval during which it is undergoing a change into simpler substances It follows that among the split products are to be found the substances which activate the white cells in the bone marrow and are responsible for their increased appearance in the blood stream While it is conceivable that urea, creatinin or amino-acids, if present in high concentration, might by their diuretic salt action reduce the water reserve of the body and produce a colloidal upset with increased protein metabolism and a resultant leukocytosis, we are not aware that they, in themselves, exert any direct action on the white cells So, lacking evidence to the contrary,

it would seem that the activating substances must belong to that large and somewhat ill defined group of intermediate products of protein cleavage comprising proteoses, peptones and polypeptids

To resume the analogy with which this paper was opened, acute water shortage results in an increase of the normal protein metabolism with a greater production of its by-products, some of which as urea, creatinin and uric acid can be measured directly. Inference would lead to the belief that other by-products, both in the noncoagulable and the coagulable fractions, must be present in increased quantities in the blood. By a further analogy, the accompanying leukocytosis bears the earmarks of a chemical attraction, a positive chemotropism exerted by certain, as yet, unidentified portions of the protein molecule, possibly through alterations in the surface tension of the white blood cells, as Detweiler⁴ believes. Such a process involves their passage in increased numbers from the bone marrow to the blood stream, from the lesser to the greater concentration of the attracting substances.

As to the question of leukocytosis as an accompanying feature in many physiologic as well as pathologic conditions, the data presented make possible the preparation of a more comprehensive general scheme than has hitherto been possible.

The increase of white blood cells seen after ingestion of a heavy meal lends itself readily to explanation on a basis of these observations. It will be recalled that following a meal the blood, for several hours, contains an increased concentration of inorganic salts, sugars and amino-acids, products of digestion, each capable of exerting a saltlike osmotic pressure and causing a diuresis. In brief, there exists a condition of dehydration, if by that term be understood either an actual water loss, an increase in the salt content or percentage of colloidal combination of the water reserve, or both. It has been suggested³ that strong salt solution produces an increased cleavage of body proteins by causing their displacement from combination with the usual water of hydration, a matter of relative osmotic pressures. It serves the need of an hypothesis in this case and will be used unamended. Following ingestion of food are found the necessary conditions for a slight increase of metabolism in the body protein. There is no direct proof that this occurs and if present it is undoubtedly small. Nevertheless, the sequels of the protein cleavage of dehydration are also present, a picture which includes a moderate leukocytosis of perhaps from 10,000 to 12,000, a rise of a few tenths of a degree in temperature and an increased urinary output.

Following prolonged or violent exercise there occurs an appreciable rise of the white blood cell count which, possibly, depends on certain of

⁴ Detweiler, H. K. Tice's Practice of Medicine, W. F. Prior Co., New York, 1920, 1:259

the forces under discussion. A considerable amount of water may escape and combustion of protein for energy may, to a certain degree, occur with, in either case, a larger production of nitrogenous bodies exerting an activating influence on the leukocytes.

No data are at hand concerning the leukocytosis of pregnancy.

To sum up the nonpathologic leukocytoses, it appears that water and salt balance may exert a hitherto underestimated influence. It is known that daily normal variations occur over a considerable latitude. Mauriac and Cabouat⁵ have carefully studied these. We have noted slight increase of white blood cell count, blood nitrogen and temperature in control dogs which were kept where some evaporation of water might occur. In short, the experimental results obtained seem to be due to an extension and intensification of forces which may cause variations in these three features within the limits of normal and are possibly associated in the maintenance of normal values.

Among pathologic increases of the white blood cells, the increase following hemorrhage should first claim our attention. Musser⁶ reviews this as a sharp rise in the polymorphonuclears due to "retention of the leukocytes in the blood stream during hemorrhage by adhesion to the vessel walls with diminution of blood volume and, presumably, an outpouring of white blood cells from the bone marrow in response to an unknown stimulus." Taylor and Lewis⁷ strongly suggest the nature of this stimulus by reporting appreciable increases in the nonprotein blood nitrogen of dogs subjected to repeated severe hemorrhages. This high protein metabolism may, in some measure, be due to changes in the water and salt balance, but seemingly other factors also play a part, as they were unable to prevent it by immediately restoring the blood volume with Ringer's solution after each hemorrhage. The almost proverbial water hunger which occurs in hemorrhage suggests that fluid has a definite place in treatment.

As regards a resemblance of the above experimental records to the picture of hemorrhage, it is repeatedly present and includes, in addition to a rising leukocyte count and blood nitrogen concentration, a falling temperature. This combination shows in the fore part of many of the charts and is followed by a recovery and rise of the temperature in the last few hours only. It appears that heat production is increased throughout which would lead to the suspicion that its rate of elimination is above normal in the early hours to later drop.

⁵ Mauriac, P, and Cabouet, P. Variations in Leukocyte Count in the Normal, *Paris med* **11** 407 (May 21) 1921.

⁶ Musser, J H, Jr. The Leukocytes After Hemorrhage, *Am J M Sc* **162** 40 (July) 1921.

⁷ Taylor, A E, and Lewis, H B. A Study of the Protein Metabolism Under Conditions of Repeated Hemorrhage, *J Biol Chem* **22** 71, 1915.

We will now discuss a possible explanation of leukocytosis in the acute bacterial infections and consider its relationship to the dehydration theory of fever as originally advanced by Balcar, Sansum and Woodyatt and later modified by ourselves

This theory urges the view that the body water reserve exists in two forms, first, free and uncombined, in which state the high specific heat renders it valuable for absorption and transportation of calories from one portion of the body to another, thus equalizing temperature, or to the surface for elimination by radiation and, secondly, in colloidal combination with proteins, glycogen and in the hydrates of inorganic salts, which destroys its ability to regulate heat. It further suggests that in infection the bacteria, through their toxins, so modify the body colloids as to largely increase their hydration capacity and thus produce a shortage of free water. Inadequately hydrated proteins commence to break down at an abnormally rapid rate and produce increased quantities of heat which is largely retained because of the lack of available water to care for it.

The case in favor of the dehydration theory, as it at present stands, may be stated as follows. In many bacterial diseases there is evidence of retention within the body during the acute febrile stage of considerable quantities of water which are more or less rapidly released as recovery ensues. To be specific, typical lobar pneumonia retains sometimes a number of liters of water during the acute stage and liberates it rapidly as sweat and urine at the crisis. Cases of colon bacillus peritonitis which recover will, if accurate account is kept of the fluid intake and output, show a similar, if less spectacular, phenomenon. Even the acute localized cutaneous or subcutaneous infections usually show an edema or water retention about them which extends far beyond the area of redness and beyond the area of actual bacterial invasion. This is best observed early, before the formation of pus with its measure of immunity, and is a localized demonstration of what may become a general condition. This retention can be explained only on the basis of some change in the state of combination in which the water is held, otherwise it would not occur. We know that an acute shortage of water will produce quite a large increase in the nonprotein blood nitrogen and this in the entire absence of any preexisting nephritis. It is due largely to two factors, first, an increase of protein metabolism with a larger production of waste nitrogen, and, second, a scarcity of water as a vehicle for excretion. Tileston and Comfort⁸ and Wells⁹ have

8 Tileston, W., and Comfort, C. W., Jr. The Total Nonprotein Nitrogen and the Urea of the Blood in Health and Disease as Estimated by Folin's Methods, *Arch Int Med* **14**:620 (Nov) 1914

9 Wells, C. W. Blood Chemistry Studies in Influenzal Pneumonia, *Arch Int Med* **26** 442 (Oct) 1920

each reported a series of pneumonia cases in which an increase of blood nitrogen is present in a large per cent Vaughan and Morse¹⁰ found in a series of peritonitis cases the same feature which may probably occur independently of intestinal obstruction These are both conditions which almost never give rise to any of the varieties of true nephritis and the only acceptable explanation of what has occurred in the cases cited, and, inferentially, what has occurred in such cases in general, seems to be that outlined It is also reasonably safe to assume that the fever of the condition is due to an increased protein catabolism of which the high waste nitrogen stands as concrete evidence

If the velocity of protein cleavage is enhanced, one would expect, in addition to the heat production, attraction of an abnormally large number of white blood cells from the bone marrow, and, true to form, both pneumonia and peritonitis show this The leukopenia sometimes seen in the stage of invasion of these diseases, particularly pneumonia with its rapid onset, resembles in some ways the leukopenia seen at the end of the first hour in the records of dogs subjected to experimental dehydration The correct explanation of this feature, from a physico-chemical standpoint, we are, at present, unable to give

Tileston and Comfort state that typhoid fever never shows an increase in the nonprotein blood nitrogen The white blood cell count is characteristically low, and consequently the condition must be exempted from the application of many of the foregoing remarks

This discussion offers more or less plausible reasons for many hitherto not well understood changes in the leukocytes Of course, the parallel rise of leukocytes and waste nitrogen seen experimentally cannot always be observed in clinical practice because of the probability that the relatively soluble urea, creatinin and uric acid may constantly be excreted through the kidneys by the intake of quantities of water too small to compensate entirely for the pathologic increase in water requirements and yet sufficient to care for a considerable portion of the waste formed The leukocytes are subject to no such excretion and consequently attain maximum values

If the condition under consideration is a bacteremia, with the most marked changes of water balance in the blood, the story ends, so far as this paper is concerned, when the leukocytes enter the circulation If the infection be a localized one with a general reaction, we may understand that toxin concentration, change of water requirements, cleavage of protein and consequent heat production would be most marked in the immediate vicinity of the offending organisms The same changes on a somewhat smaller scale would be present in the blood The leukocytes, always moving from lesser to greater concen-

10 Vaughan J W, and Morse, P F Blood Nitrogen Estimations in Genito-Urinary and Abdominal Conditions, Arch Surg 3 405 (Sept) 1921

tration of the activating nitrogenous bodies, might be expected to leave the circulation at a point near the area of infection and following the ever fresher trail arrive in the midst of the bacteria in increasing numbers with eventual engulfment of the organisms, each a center of disturbance, thus leading to phagocytosis and pus formation

SUMMARY

A picture has been drawn which portrays the leukocytes and fever (if one wishes to consider that an immune reaction) as a second line of defense against infection, responding only after invasion due to a let down of primary humoral immunity, if such it be, and then responding to non-specific stimuli which arise from quantitative alteration in the bodily metabolism rather than directly from the infecting organisms, the same stimuli which on a smaller scale produce variations of normal values in the absence of infection

CONCLUSIONS

1 An experimental leukocytosis results from production of an acute water shortage with corresponding increases of body temperature and nonprotein blood nitrogen

2 This leukocytosis has many features in common with the physiologic increases of digestion and exercise

3 It throws added light on the mechanism of leukocytosis in hemorrhage, and is corroborative evidence of the essential correctness of the dehydration theory of fever

We wish to express our indebtedness to Dr P F Morse for the use of laboratory equipment and for many valuable suggestions, and to Drs C L Douglas and E S Crump for kindly interest and thoughtful courtesies

BLOOD PRESSURE AND PULSE RATE REACTIONS *

SECOND PAPER

T ADDIS, M D

SAN FRANCISCO

During the late war there was an urgent need for some objective test by which the presence and the degree of circulatory disability could be measured. The observations on which this paper is based were made in the attempt to supply this need.

The great majority of men with organic heart disease were rejected before admission to the army, but under the regulations issued for the medical examination of drafted men, it was not possible to exclude those who suffered from the condition known as irritable heart, neuro-circulatory asthenia or effort syndrome, though a considerable percentage was later found to be incapable of active service. In England, Lewis developed a series of graduated drills by which the capacity of these men for service could be estimated. I used this system of exercises at Camp Lewis, both in normal individuals and in cases of irritable heart, but after some months it was discarded because the results were uncertain and the method required too much time. This was chiefly due, I believe, to the fact that Lewis was dealing with trained soldiers, while we had raw recruits. An essential for the success of his plan is that the exercises be carried out with sharpness and precision, so that the amount of effort entailed is more or less uniform. With untrained men, especially men suffering from cardiac, vasomotor and nervous symptoms, we did not succeed in attaining this uniformity. After a considerable experience of military discipline response to orders is almost involuntary. Without this experience movements are slowed and inadequately performed at the first onset of fatigue. The amount of work done varies rather with the psychic state of the individual than with his physical capacity. Time also was of importance in our case. Circumstances were such as to call for a decision in days rather than in weeks.

Efforts were made to use the exercise test recommended from Washington, D C. This depends on the effect on the pulse rate of change of position and of hopping 100 times. Since no normal standards were given, the pulse rates of 1,000 normal recruits were counted throughout a test which was a slight modification of the official test. From these data statistical standards of normality were prepared¹. But this method was also abandoned, for reasons which will be discussed in this paper. The pulse rate method was still further developed by

* From the Medical Department of Stanford University Medical School

1 Addis J A M A 72 181 (Jan 18) 1919

observing the effect of hopping, first 100, then 200, 300, 400 and 500 times without intermission, except for the short intervals during which the pulse was counted. This test demonstrated that even persons with marked symptoms were capable of the quite severe exertion which this amount of exercise entails, but otherwise it was not found to be of much value.

The test which was actually used developed as a result of a trial of Crampton's method² in which observations of systolic pressure as well as of pulse rate are made before and after rising from the recumbent to the erect position. First, while the subject is lying down, the pulse rate is counted for quarter minute intervals until a constant pulse rate is attained. The systolic pressure is then taken. After the subject stands up the pulse rate is again counted until it becomes constant and then the second systolic pressure reading is made. The results were found to be very variable, and in order to find the causes of this high degree of variability, a consecutive series of blood pressure and pulse readings were made simultaneously at quarter minute intervals before and after the subject altered his position. It then became clear that one reason for the inconstancy of the results lay in the varying time required for the pulse rate to become constant after standing. If this time were very short, a fall in systolic pressure was frequently found. If it took a little longer the pressure was often higher than when the subject was lying down and later still it fell to a more or less constant level. On examining the charted records of these experiments it was seen that the greatest change in systolic pressure occurred immediately after standing and that this effect was usually missed altogether by waiting until the pulse rate became constant.

The system of simultaneous pressure and pulse rate measurements was then applied to the test which had been used in the pulse rate work. Twelve consecutive pressures and pulse rates were taken, six before and six after exercise. Exercise consisted of 100 hops timed by a metronome striking at a rate of 120 to the minute. Pulse rates were counted over fifteen second periods, and each pressure reading was made as nearly as possible in the middle of these periods, which were timed by a watch attached to the sphygmomanometer. A mercury instrument was used which had a 5 inch canvas backed arm band under which a special stethoscope bell was fitted. One hand of the observer was thus free to make the air pressure adjustments while the other held the instrument. The systolic pressure was read at the first appearance of sound as the mercury fell. But in many cases after exercise the sound of the beat of the forcibly pulsating artery against the upper edge of the arm band could be heard, and the first accentuation of sound was then taken as the signal to read the systolic pressure. The diastolic pressure was read

2 Crampton. New York M. J. 98 916, 1913

at the commencement of the fourth phase, or at the disappearance of sound when no fourth phase could be distinguished. The blood pressures were taken by myself, the pulse rates by an assistant, usually with a stethoscope over the heart. Simultaneous counts by two assistants, one from the wrist and one from the heart, showed that a considerable degree of accuracy was quickly attained. Another assistant acted as recorder. The effect of change of position was determined both before and after exercise by having the subject lying flat on his back for the first three fifteen second periods and standing erect for the next three periods. The whole test required 230 seconds, the first forty-five lying down before exercise, the second forty-five standing before exercise, the hopping covered fifty seconds and was followed by lying and standing position for two forty-five second periods. Twelve observations were thus obtained from each subject under four successively changing conditions.

SECTION I

THE REACTION OF THE CARDIOVASCULAR SYSTEM IN NORMAL INDIVIDUALS

The average reaction of the cardiovascular systems of normal individuals and its variability under this test was first determined. For this purpose 300 soldiers between the ages of 21 and 31 were chosen. They stated that they were in good health at the time they were examined and none had suffered from any recent illness or infection. All had undergone two or more months of intensive physical training. The averages, coefficients of variation (the standard deviations expressed as percentages of their respective averages) are given in Tables 1 and 2. The frequency distributions for each of the twelve periods will be found in Table 11. The averages are charted in Figure 1.

The conditions of this test constitute in reality two different tests, for the cardiovascular system has to adapt itself to two diverse forms of strain. There is the strain of adjustment to muscular exercise which requires that the nervous system, the heart and the vessels should work together to send a greater supply of blood to the active muscles. And there is the strain, both before and after exercise, of adjustment to a sudden change from a horizontal to a vertical position of the body. This requires an intricate mechanism of adaption from the cardiovascular system to prevent the force of gravity from interfering with the uniformity of blood distribution. Therefore in using the pressure and pulse rate measurements on normal individuals for establishing standards we must distinguish between the effect of exercise and the effect of change of position, and must choose those periods in the series of measurements at which the effects are most marked. It is apparent

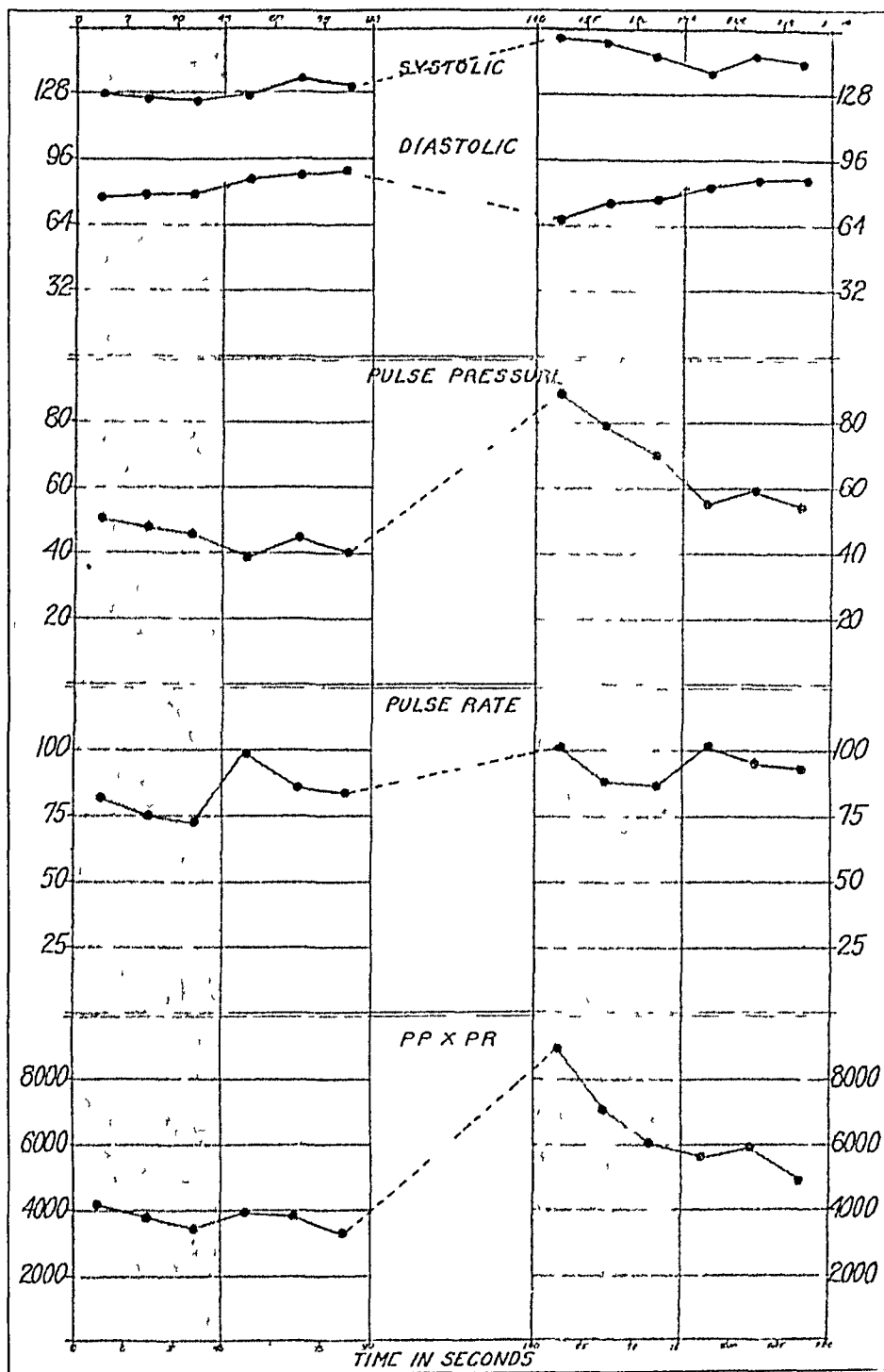


Fig 1—Normal Persons Average blood pressure and pulse rate of 300 normal persons showing the effect of change of position and of exercise. The darker shaded areas represent the period during which the subjects were lying down, the lighter areas the period during which they stood up while the unshaded portion indicates the time during which 100 hops were taken.

from Figure 1 that the most pronounced effect of exercise is seen in the first period after exercise, and that the change from the recumbent to the erect position occurs in the first periods after standing. These are the points at which the effects of the two strains should be estimated. The base from which the degree of effect should be measured is the third period in the lying position in the case of exercise, and the periods

TABLE 1—AVERAGES OF 310 NORMALS

	Time in Seconds													
	0	15	30	45	60	75	90	140	155	170	185	200	215	230
	Lying			Standing			Hop ping	Lying			Standing			
Systolic	127	127	125	126	134	131		156	153	147	138	145	141	
Diastolic	78	80	81	86	90	91	68	74	78	84	87	87		
Pulse pressure	50	47	44	39	44	41	88	79	70	55	59	54		
Pulse rate	80	76	74	99	84	82	101	90	86	102	95	93		
P P × P R	3980	3700	3380	3950	3790	3380	9030	7190	6040	5630	5930	5050		

immediately preceding standing in the case of the strain induced by change of position. The average effect can be deduced by difference from the averages given in Table 1. Thus exercise raises the systolic pressure from 125 to 156, an increase of 31 mm of mercury while standing raises the systolic pressure 1 mm before exercise and is accompanied by a fall of 9 mm after exercise. It would seem then that normality might be expressed as all those differences which lie within the range of the average differences + and — some measure of variability of the measurements.

TABLE 2—COEFFICIENTS OF VARIATION $\frac{\sigma}{Av} \times 100\%$
300 Normals

	Time in Seconds													
	0	15	30	45	60	75	90	140	155	170	185	200	215	230
	Lying Before Exercise, %			Standing Before Exercise %			Hop ping	Lying After Exercise, %			Standing After Exercise, %			
Systolic	13	13	12	13	13	12		13	13	14	13	13	13	
Diastolic	14	14	12	15	13	13		17	15	14	14	14	13	
Pulse pressure	28	28	29	27	27	26		21	22	23	29	25	26	
Pulse rate	16	16	16	16	18	18		15	15	15	15	17	17	
P P × P R	38	36	36	33	36	34		28	28	30	33	31	33	

But to adopt this plan would be to neglect the possibility that the level of the base may influence the difference induced by strain. It may be that exercise produces a greater difference in a subject with low blood pressure and slow pulse than it would if before the exercise the cardiovascular system were already in a state of hyperactivity. If that is so each initial level will have its own peculiar limits of variation.

In order to decide this preliminary question the data were arranged so that the amount of difference induced in subjects with initially low pressure and slow pulse could be compared with the difference produced in subjects with relatively high pressure and rapid pulse. The average

TABLE 3—RELATION BETWEEN THE INITIAL LEVEL OF PRESSURE OR PULSE RATE AND THE EFFECT PRODUCED BY STRAIN

Group	Effect of Exercise			Effect of Change from Horizontal to Vertical Position					
	Number of Subjects in Group	Average of Group Before Exercise	Change in Average of Group After Exercise	Standing Before Exercise			Standing After Exercise		
				Number of Subjects in Group	Average of Group Before Standing	Change in Average of Group After Standing	Number of Subjects in Group	Average of Group Before Standing	Change in Average of Group After Standing
Systolic Pressure									
101-110	36	109	+30	36	109	+3			
111-120	78	118	+31	78	118	+2	25	119	-3
121-130	75	128	+33	75	128	-2	40	128	-5
131-140	50	138	+30	50	138	-4	54	139	-5
141-150	28	148	+32	28	148	-2	56	149	-11
151-160							47	158	-13
161-170							42	168	-15
Diastolic Pressure									
51- 60							24	59	+9
61- 70	61	69	-10	61	69	+7	86	69	+9
71- 80	110	79	-12	110	79	+6	105	78	+3
81- 90	80	88	-14	80	88	+4	61	88	+5
91-100	32	98	-17	32	98	+2			
Pulse Pressure									
21- 30	41	28	+46	41	28	+1			
31- 40	93	38	+44	93	38	-3			
41- 50	101	48	+41	101	48	-7	30	49	-8
51- 60	43	57	+43	43	57	-11	58	58	-10
61- 70							77	68	-13
71- 80							60	78	-16
81- 90							32	88	-19
91-100							22	98	-21
Pulse Rate per Minute									
53- 60	33	58	+27	33	58	+19			
61- 68	77	66	+26	77	66	+19			
69- 76	84	74	+29	84	74	+18	64	74	+16
77- 84	43	82	+24	43	82	+16	74	82	+16
85- 92	36	89	+29	36	89	+19	71	90	+14
93-100							38	97	+15
P P × P R									
1000-1999	37	1653	+4522	37	1653	+777			
2000-2999	85	2595	+5235	85	2595	+520			
3000-3999	107	3425	+5825	107	3425	+245	24	3543	+225
4000-4999	37	4375	+6075	37	4375	-40	53	4452	+ 83
5000-5999	25	5455	+6675	25	5455	-250	67	5404	-379
6000-6999							58	6343	-256
7000-7999							40	7412	-955
8000-8999							26	8419	-843

differences for groups with progressively increasing initial levels are given in Table 3

In the case of the $P \times P \times P \times R$ product and also of the pulse pressure and the diastolic pressure, the absolute difference induced by strain is shown in Table 3 to be dependent on the level from which the difference is measured. On the other hand, the pulse rate figures show no

dependence and in the case of the systolic pressure there is an approximately uniform increase after exercise whether the initial level is low or high

Porter and Richardson³ made a series of observations on various species of animals in order to determine the effect of variations in the initial level of mean blood pressure on the absolute increase caused by a uniform stimulus. They found that with initial pressures from 20 to 160 the increase was approximately the same whether the initial pressures were high or low. But neither their figures, nor those given here for the systolic pressure after exercise are sufficiently numerous to exclude the possibility of a slight degree of dependence. For the changes produced by strain in the different groups are as constant for the pulse rate as for the systolic pressure, and yet when a larger number of observations are dealt with it can be demonstrated that the higher the original level of pulse rate the less is the absolute increase produced

TABLE 4—RELATION BETWEEN THE INITIAL LEVEL OF PULSE RATE AND THE EFFECT PRODUCED BY STRAIN. PULSE RATE PER MINUTE FROM DATA ON 1,000 NORMAL RECRUITS

Group	Effect of Exercise			Effect of Change of Position Standing Before Exercise		
	Number of Subjects in Group	Average of Group Before Exercise	Increase in Average of Group After Exercise	Number of Subjects in Group	Average of Group Before Standing	Increase in Average of Group After Standing
60-69	193	65	+33	193	65	+20
70-79	305	74	+29	305	74	+17
80-89	358	83	+28	358	83	+15
90-99	78	94	+26	78	94	+14

by exercise and change of position. These data were obtained from counts made on 1,000 normal recruits under conditions very similar to those described here.¹

The "probable difference between the averages" of the increases of consecutive groups were calculated and were found to be several times smaller than the actual differences. This fact taken in conjunction with the existence here of a double series both showing a progressive decrease excludes the possibility that these differences can be accidental.

If an adequate number of observations were available, it might be found that a similar minor degree of dependence on initial level existed in the case of the systolic pressure also. But since in any case it has been shown that the original level is a factor in the change produced in all the other measurements, it is essential that the records after strain be grouped in accordance with the order of magnitude of the level before strain. It is only from the averages of these groups and

3 Porter and Richardson. *Am J Physiol* 23 131, 1908

from a measure of their variability that a standard may be deduced which will be applicable to all cases no matter how variable the level before strain

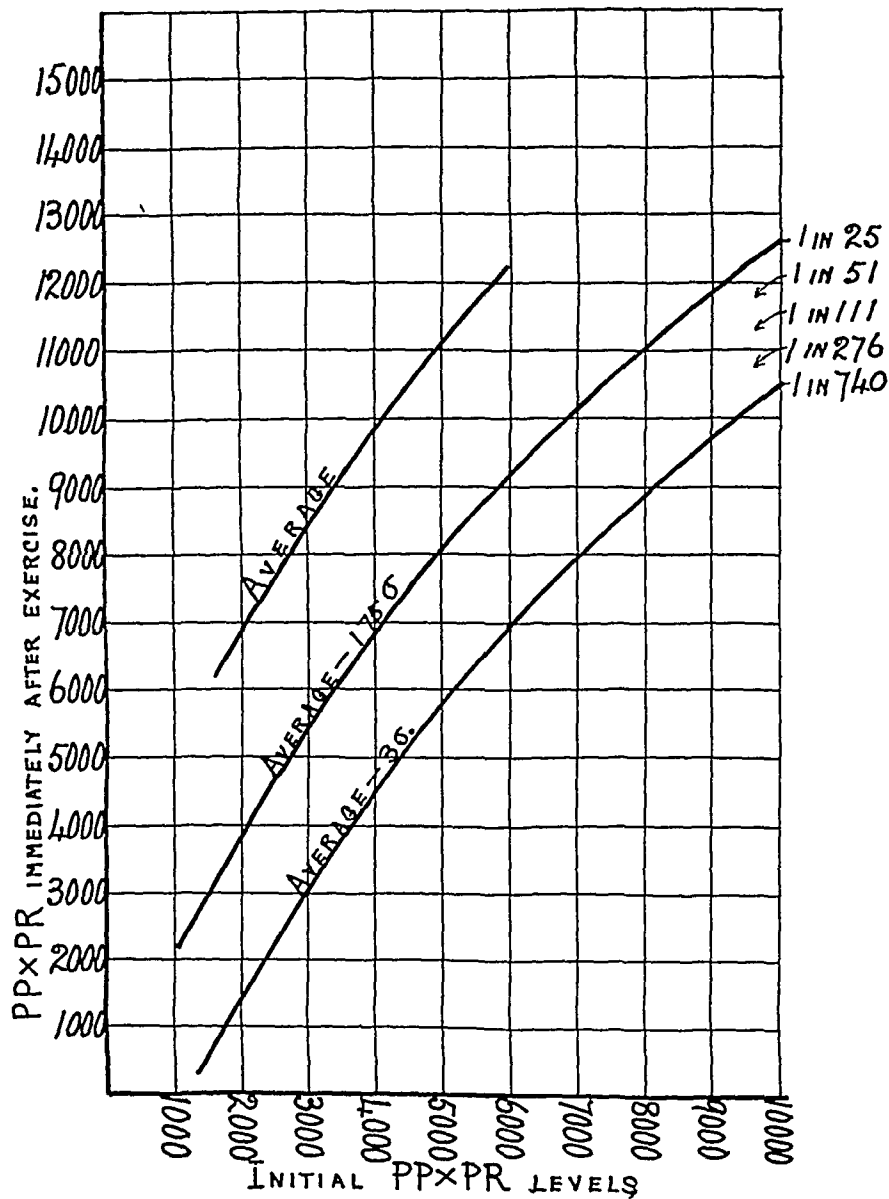
The usual measure of variability—the standard deviation—is applicable only in the event of the data grouping themselves in a “normal”

TABLE 5—AVERAGES AND STANDARD DEVIATIONS AFTER STRAIN ARRANGED IN ACCORDANCE WITH THE LEVEL OF PRESSURE OR PULSE RATE BEFORE STRAIN

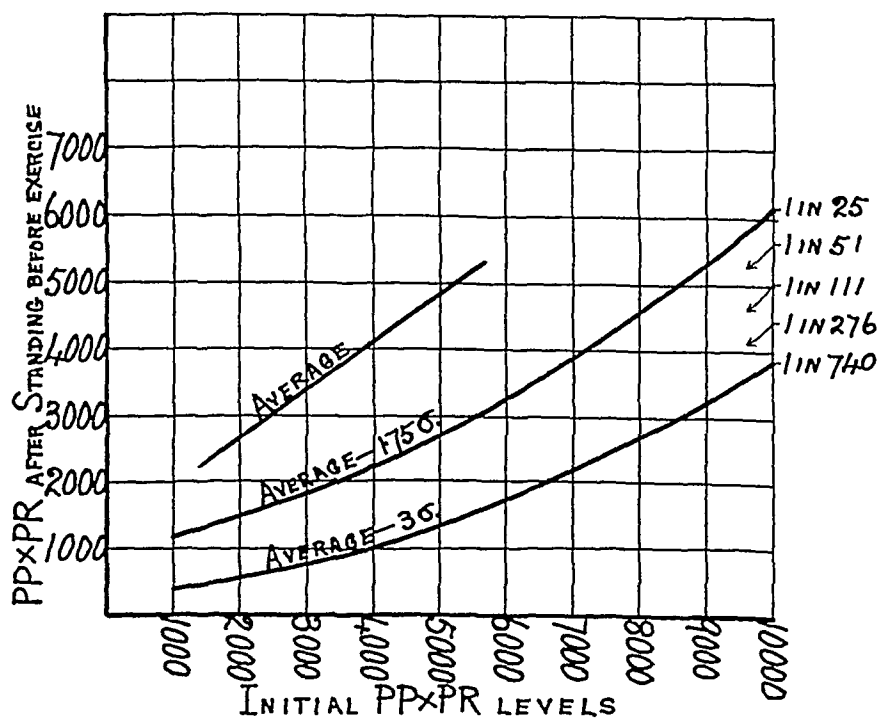
Group	Basal Average		After Strain						Basal Average		After Strain	
	Before Exercise or Standing		After Exercise				After Standing		Before Standing After Exercise		After Standing After Exercise	
	Third Period		First Period		Third Period		First Period		Third Period		First Period	
	No	Av	Av	σ	Av	σ	Av	σ	No	Av	Av	σ
Systolic Pressure												
101-110	36	109	138	± 13	131	± 12	112	± 11				
111-120	78	118	149	± 13	139	± 11	120	± 11	25	119	117	± 8
121-130	75	128	161	± 15	153	± 14	126	± 11	40	128	123	± 12
131-140	50	138	168	± 12	160	± 11	134	± 13	54	139	134	± 10
141-150	28	148	180	± 11	170	± 14	147	± 15	56	149	138	± 11
151-160									47	158	145	± 13
161-170									42	168	153	± 15
Diastolic Pressure												
51- 60									24	59	68	± 9
61- 70	61	69	60	± 9	69	± 8	76	± 8	86	69	78	± 9
71- 80	110	79	68	± 9	76	± 8	85	± 9	105	78	82	± 7
81- 90	80	88	73	± 10	82	± 11	92	± 10	61	88	94	± 9
91-100	32	98	81	± 11	89	± 10	99	± 7				
Pulse Pressure												
21- 30	41	28	74	± 15	54	± 13	29	± 8				
31- 40	93	38	83	± 15	65	± 11	36	± 8				
41- 50	101	48	90	± 13	72	± 13	41	± 10	30	49	41	± 9
51- 60	43	57	102	± 13	83	± 13	47	± 11	58	58	48	± 10
61- 70									77	68	55	± 10
71- 80									60	78	62	± 13
81- 90									32	88	69	± 15
91-100									22	98	78	± 16
Pulse Rate												
53- 60	33	58	85	± 10	71	± 6	76	± 10				
61- 68	77	66	92	± 8	79	± 9	85	± 8				
69- 76	84	74	102	± 11	86	± 8	92	± 8	64	74	90	± 10
77- 84	43	82	106	± 11	89	± 7	97	± 7	74	82	98	± 8
85- 92	36	90	118	± 11	100	± 9	109	± 10	71	90	104	± 10
93-100									38	97	112	± 9
P P \times P R												
1000-1999	37	1653	6175	± 2093	4045	± 1183	2430	± 650				
2000-2999	85	2595	7830	± 1750	5180	± 1162	3115	± 830				
3000-3999	107	3425	9250	± 1769	6195	± 1338	3670	± 940	24	3545	3770	± 832
4000-4999	37	4375	10450	± 1766	7125	± 1225	4335	± 1255	53	4452	4535	± 924
5000-5999	25	5455	12130	± 1835	8500	± 1667	5205	± 1080	67	5404	5025	± 1027
6000-6999									58	6343	6087	± 1283
7000-7999									40	7412	6457	± 1500
8000-8999									26	8419	7576	± 1867

curve The frequency distributions given in Table 11 show that this may be assumed to be the case for blood pressure and pulse rate observations

In Table 5 the averages and standard deviations for the periods best adapted for revealing the effect of strain are given The data in



Part 1



Part 2

Fig 2.—Standards derived from observations on 300 normal persons. The upper part of the figure is a standard for the $PP \times PR$ product immediately after exercise. Since the effect of exercise depends in part on the level of the product before exercise, the $PP \times PR$ observed in the third period while lying down is plotted along the abscissa, so that the average and variability for any initial level may be determined. The chart shows that with an initial product of 2,000, the average product after exercise will be 6,860, with an initial product of 5,000, the product after exercise will be 11,100, and so on. If any observed product falls below the average on the upper curve (the average — 175 times the standard deviation), the odds are that one out of every twenty-five normals might have as low or a lower product. If the observed product falls on the lower curve (the average — 3 times the standard deviation) the odds are that only one out of every 740 normals would have as low or a lower product. The odds for products falling between the two curves are indicated on the chart. Products above the upper curve may very well be “normal.” Products below the lower curve are almost certainly “abnormal.” Those which lie between are doubtful in varying degree according to their degree of deviation from the average. The lower part of the figure is a similar standard for $PP \times PR$ products in the first period after standing before exercise.

the periods before strain were grouped in accordance with their order of magnitude, and the corresponding measurements after strain for each group were averaged and the standard deviation determined. Thus, for instance, the systolic pressures after exercise of all those individuals whose systolic pressure before exercise lay between 101 and 110, were averaged, and so on. From these figures standards of any degree of rigidity may be obtained. For practical purposes it may be regarded as almost certain that no normal individual will deviate more than ± 3.0 times the standard deviation from the average. The odds are that only one individual out of 740 will vary as much or more than this from the mean. With lesser degrees of deviation the chances that the measurement might be such as would be given by a normal individual rapidly increase until at the average ± 1.75 times the standard deviation the odds are that one out of every twenty-five normals might deviate so far from the average. Between these two limits lie the cases which may be either normal or abnormal, the chances varying according as they approach the lower or the upper limit. In cases beyond the limit farthest from the average there is practically no chance of normality, in cases nearer the average than the other limit, the chances of normality are so considerable that there is not sufficient reason for raising the hypothesis of abnormality.

In Figure 2 these limits are charted from smoothed curves derived from the data given in Table 5. In order to save space only the limits for the $P \cdot P \times P \cdot R$ product have been charted, and only the limits below the average after exercise and change of position have been defined because these standards are sufficient for the grading of the more important abnormalities found in the patients we examined. For cases with other types of abnormality similar standards can be easily prepared from Table 5.

SECTION II

THE SIGNIFICANCE OF THE PRESSURE AND PULSE RATE REACTIONS OF NORMAL INDIVIDUALS

In this section the reasons why exercise and change of position should produce the effects on pressure and pulse rate which we have noted are considered. The effects under consideration will be more easily followed by reference to Figure 1. In this chart, and in all the others given in this paper, the darker shading indicates that the subjects were lying down, the lighter that they were standing. The unshaded portion of the chart is the period during which they were hopping. The curves indicate that exercise increases the pulse pressure, and the pulse rate, and markedly increases the $P \cdot P \times P \cdot R$ product. Changing from the recumbent to the erect position decreases the pulse pressure, increases the pulse rate, and has no very definite effect on the

P P \times P R product Before attempting any discussion of these general effects special experiments were carried out in which the influence of progressively increasing increments of work and the effect of several modifications in the position of the body were determined in

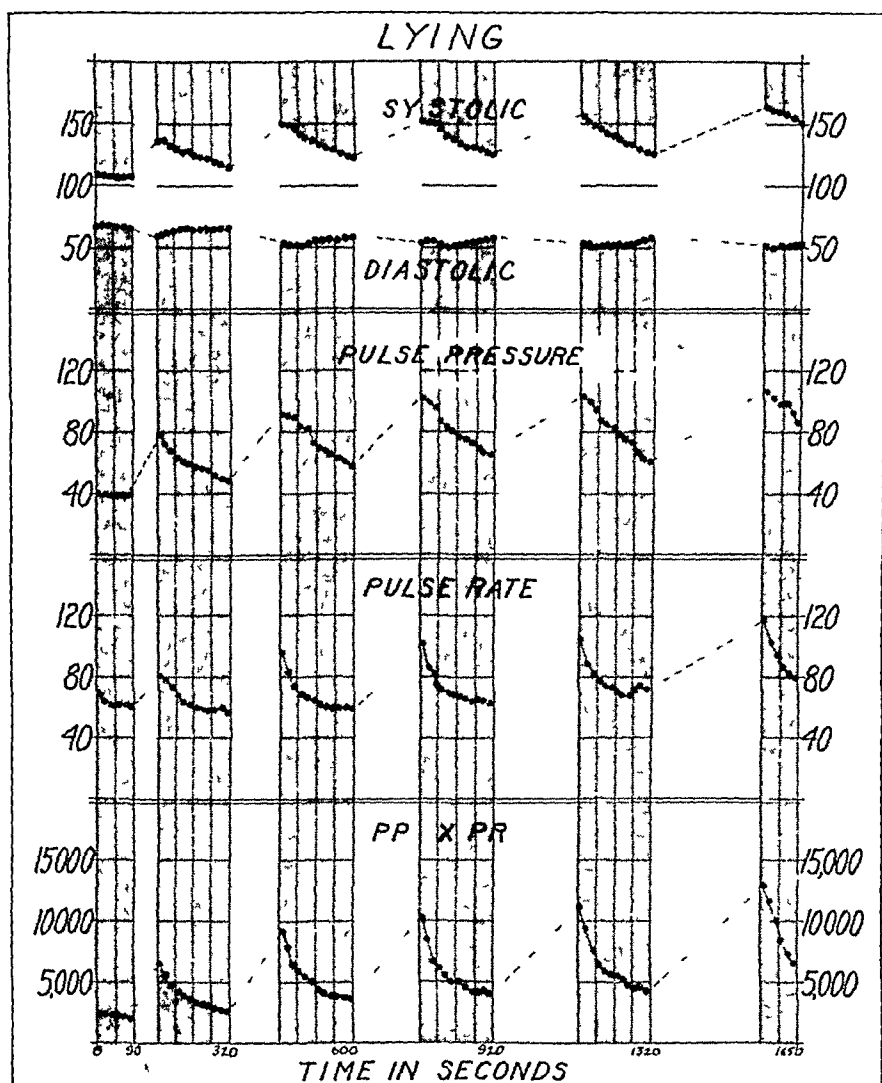


Fig 3—Lying Average blood pressure and pulse rate reactions of a group of five normal persons observed while they were lying down in the intervals between increasing amounts of exercise This figure should be compared with Figure 4 in which the reactions of the same group are charted from observations made while they were standing It will be noted that there is little difference between the PP \times PR curves in this figure and in Figure 4 But the pulse pressure is higher and the pulse rate lower in the lying than in the standing position

the hope that the more pronounced pressure and pulse rate effects thereby produced would facilitate the interpretation of the results

These special experiments were simply a continuation and intensification of the exercise conditions under which the average effects shown

in Figure 1 were obtained, combined with various alterations in the position of the body. Immediately after the completion of the observations following 100 hops, the subjects hopped 200 times and after the same intervals for the measurement of the pressure and pulse rate 300

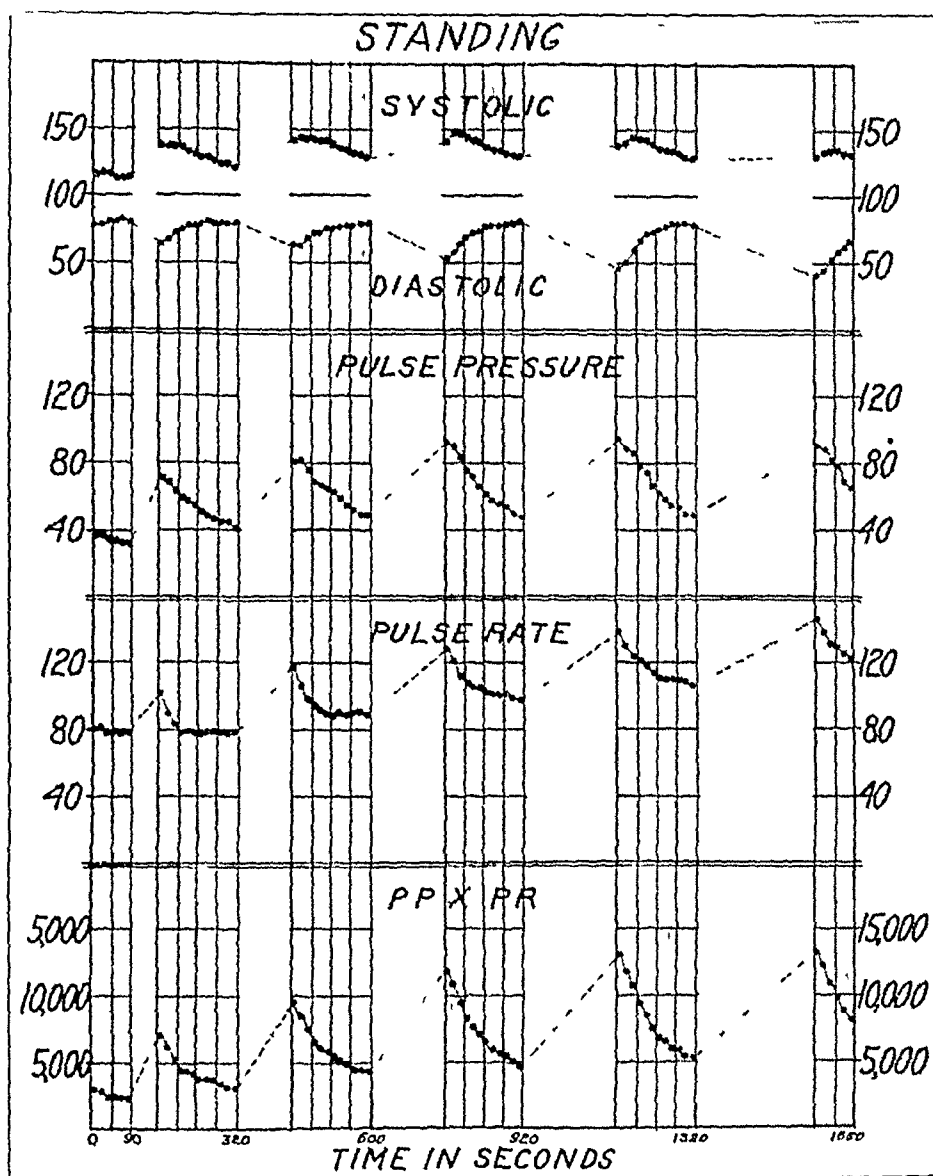


Fig 4—Standing Average blood pressure and pulse rate reactions of a group of five normal persons observed while they were standing up in the intervals between increasing amounts of exercise. This figure should be compared with the results on the same group observed while they were lying down (Fig 3). The systolic pressure curve shows what has been described as a "delayed rise in systolic pressure after exercise." This is seen only when the subjects are standing up. It is absent from Figure 3 where the subjects were lying down.

and then 400 and lastly 500 hops were taken. In this manner a consecutive series of observations were made covering a period of nearly half an hour and the effect of the progressively increasing amount of work was determined. The position of the body was varied by having

the subjects lie down or stand up between the hopping, or alternately lie down and stand up at intervals of forty-five seconds between the exercises. A group of five normal individuals were observed during lying, standing, and alternate lying and standing experiments, and in another group of three normals ten experiments were performed lying on a tilting table, head down, at an angle of 23 degrees and compared with ten experiments on the same subjects in which the readings were made while they were standing⁴. The averages obtained in the experiments in which one position was continuously maintained are charted in Figures 3, 4, 5 and 6. The alternate lying and standing experiment will be given later when the effect of change of position is discussed.

The effect of exercise on the circulation has been studied by methods which allow of an accurate measurement of changes in the volume flow of blood, i.e., of the amount of blood flowing through the aorta per unit of time. This work has been recently collected and summarized by Bainbridge⁵. It is agreed that two changes occur in the heart's action. There is an increase in the amount of blood discharged at each systole and there is an increase in the number of systoles. The combined effect of both of these changes is an increase in the amount of blood flowing per unit of time through the aorta. Lindhard⁶ and Newburgh and Means⁷ found that when muscular work was performed there was a direct proportion between the amount of work done, and the increase in the volume flow of blood. This gives the most complete and final answer to the question as to the general circulatory effect of exercise, so that all we need do is to study our pressure and pulse rate data in order to find whether there is anything in them which might have enabled us to arrive at the correct conclusion if we had had to depend on them alone. If the volume flow of blood had been measured, and plotted on our charts it would have shown a progressive increase with each increment of work, so that if any pressure or pulse rate data can be taken as an index of changes in volume flow the curves derived from them must also show this progressive increase.

When the charts are studied in the light of these facts it is clear that the only curves which can approximate to changes in volume flow of blood are the $P \cdot P \times P \cdot R$ curves. In all the four charts, irrespective of the position of the body, there is a progressive increase as the work done increases. This is what might have been expected on a priori grounds, for the volume flow of blood per minute is the product

4 An experiment of this sort was made on this group while they sat down between the exercises. The results closely resembled those obtained in the standing experiments.

5 Bainbridge. *The Physiology of Muscular Exercise*, 1919, Oxford Press.

6 Lindhard. *Arch f d ges Physiol* **161** 233, 1915.

7 Newburgh and Means. *J Pharmacol & Exper Therap* **7** 441, 1915.

of the systolic output per beat and the number of beats per minute. The pulse pressure is produced by the systolic output of the heart, and, other things being equal, will increase in direct proportion to any increase in the amount of blood discharged into the aorta with each

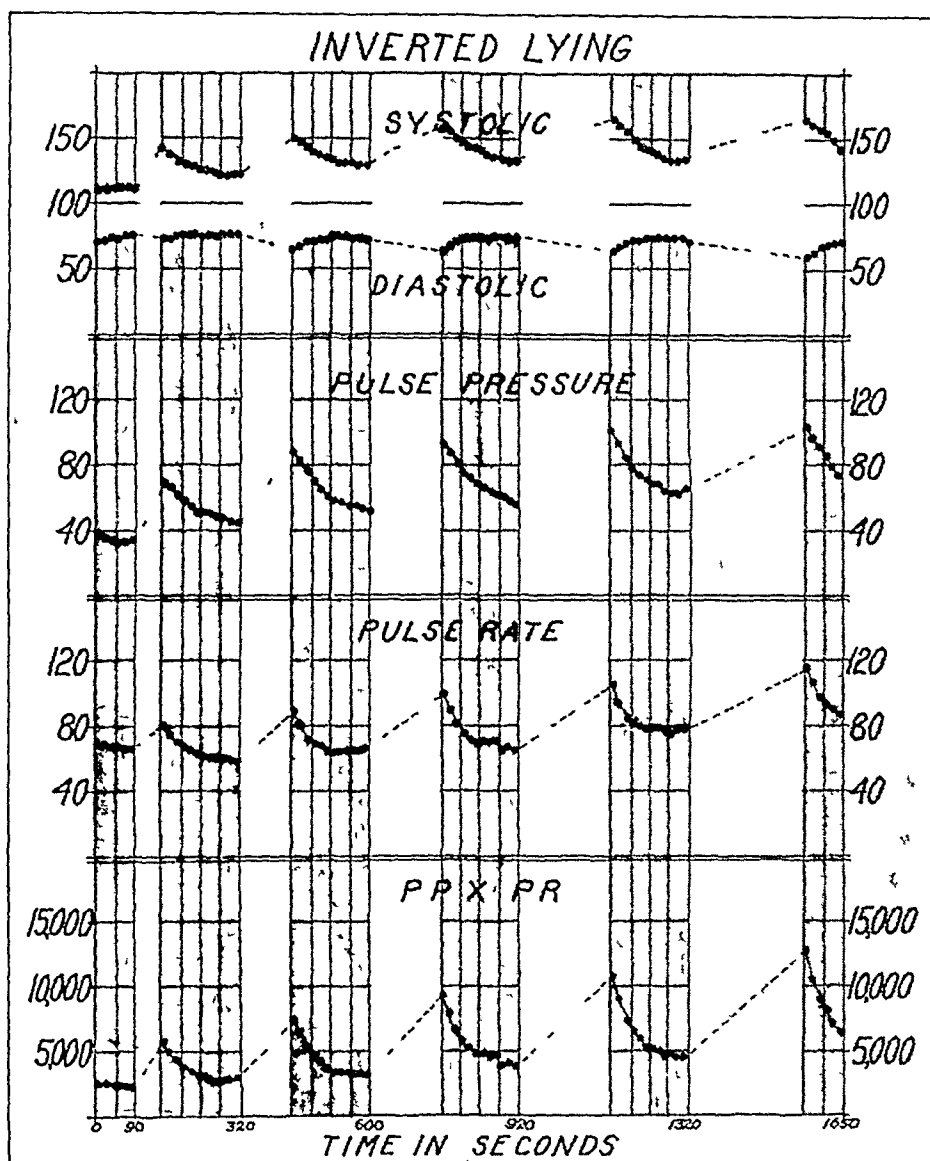


Fig 5—Inverted Lying Average blood pressure and pulse rate reactions derived from ten experiments on three normal persons while they were lying inverted on a table at an angle of 23 degrees in the intervals between increasing amounts of exercise

This figure should be compared with the results on the same group observed while they were standing (Fig 6). It shows that during inverted lying the pulse pressure is higher and the pulse rate lower than in the standing position, though there is not much difference between the $P \times P \times P R$ curves in the two experiments

systole of the heart. The $P \times P \times P R$ product may, therefore, be expected to follow changes in volume flow of blood more closely than any other pressure or pulse rate measurements. These charts show that what might be expected does actually occur.

If any one of these charts is studied alone, it might appear that pulse pressure or pulse rate alone might follow the changes in volume flow, for both of these curves increase with each increment of work. But if the curves in the lying experiments are compared with the same curves in the standing experiments, it will be noticed that the position of the body has a considerable influence on the degree of increase

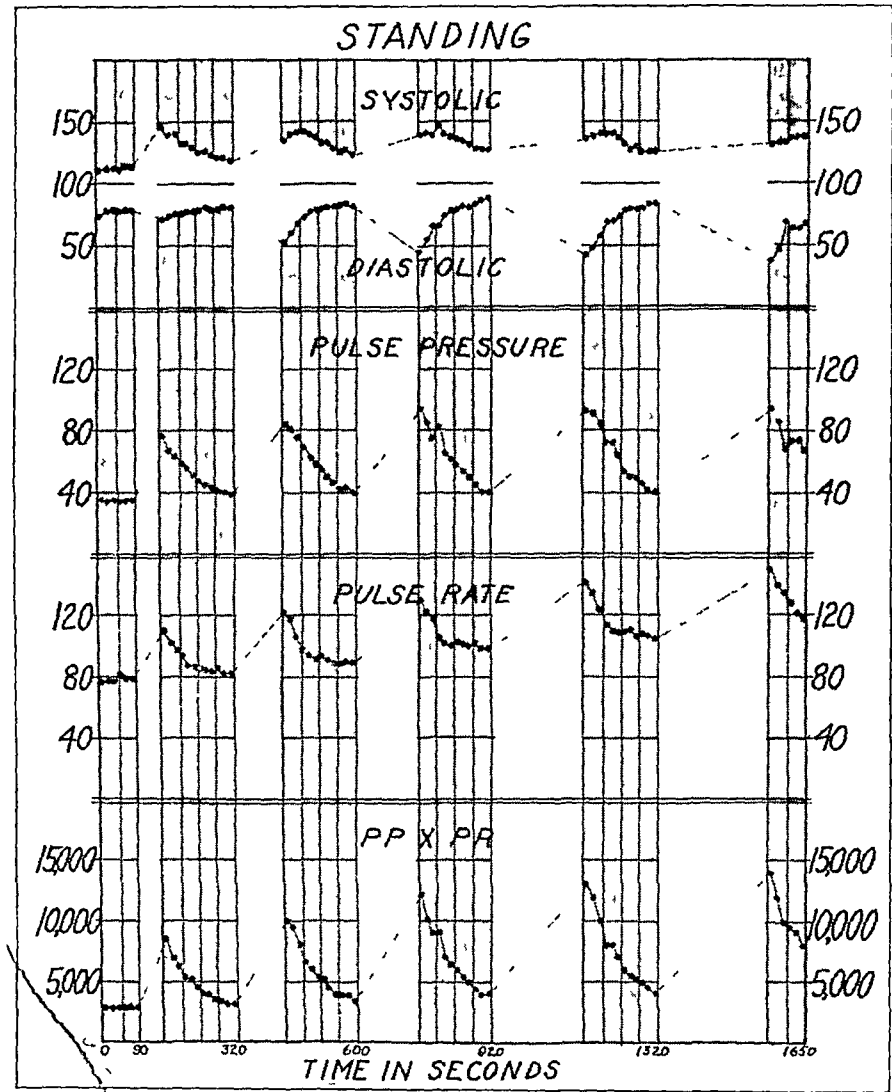


Fig 6—Standing Average blood pressure and pulse rate reactions derived from ten experiments on three normal persons while they were standing in the intervals between increasing amounts of exercise For comparison with Figure 5

shown by each of them. In Table 6 the first readings after exercise in the lying position are compared with the first readings after exercise in the standing position, and in Table 7 the first readings after exercise while the subjects were lying inverted are contrasted with readings on the same subjects made at the same point while they were standing.

In both comparisons the pulse pressure increase is less and the pulse rate increase is greater when standing than when lying. The reason for these differences will be discussed when the effect of change of position is considered. They are mentioned here in order to show that neither pulse pressure nor pulse rate alone can be adequate measures of the effect of exercise because they are influenced by a factor extraneous to the exercise. So also it may be said that neither systolic output

TABLE 6—EFFECT OF EXERCISE. COMPARISON OF OBSERVATIONS MADE IMMEDIATELY AFTER EXERCISE ON SUBJECTS WHO WERE LYING DOWN, WITH OBSERVATIONS MADE AT THE SAME POINT ON THE SAME SUBJECTS WHEN THEY WERE KEPT STANDING

Exercise Number of Hops	Position	Blood Pressure		Pulse Pressure	Pulse Rate	P P / P R
		Systolic	Diastolic			
100	Lying	138	60	78	83	6,404
	Standing	147	70	77	111	8,556
200	Lying	150	52	98	95	9,324
	Standing	130	52	84	122	10,240
300	Lying	154	50	104	102	10,670
	Standing	140	45	95	131	12,436
400	Lying	158	50	108	107	11,600
	Standing	136	44	92	142	13,100
500	Lying	162	51	111	118	13,160
	Standing	132	38	94	151	14,100

TABLE 7—EFFECT OF EXERCISE. COMPARISON OF OBSERVATIONS MADE IMMEDIATELY AFTER EXERCISE ON SUBJECTS WHO WERE LYING INVERTED HEAD DOWN, WITH OBSERVATIONS MADE AT THE SAME POINT ON THE SAME SUBJECTS WHEN THEY WERE KEPT STANDING

Exercise Number of Hops	Position	Blood Pressure		Pulse Pressure	Pulse Rate	P P / P R
		Systolic	Diastolic			
100	Lying Inverted	144	72	72	81	5,830
	Standing	136	64	72	101	7,275
200	Lying Inverted	153	66	87	88	7,650
	Standing	142	61	81	117	9,400
300	Lying Inverted	160	65	95	101	9,600
	Standing	144	53	92	129	11,800
400	Lying Inverted	167	63	104	105	10,900
	Standing	130	45	94	140	13,120
500	Lying Inverted	167	58	110	116	12,770
	Standing	132	41	91	148	13,350

per beat nor pulse rate alone are measures of the actual changes in volume flow of blood. These changes can be measured only by the product of the systolic output per beat and the number of beats per unit of time. And in the data we have obtained in these experiments the only curves which can coincide with the progressive and uniform increase in volume flow of blood which we know occurred, are the curves derived from the product of the pulse pressure and the pulse rate.

It may be concluded, therefore, that an attempt to determine the effect of exercise on the circulation from pressure and pulse rate data alone could have been successful only if it had been based on the changes in the $P \times P \times P \times R$ product

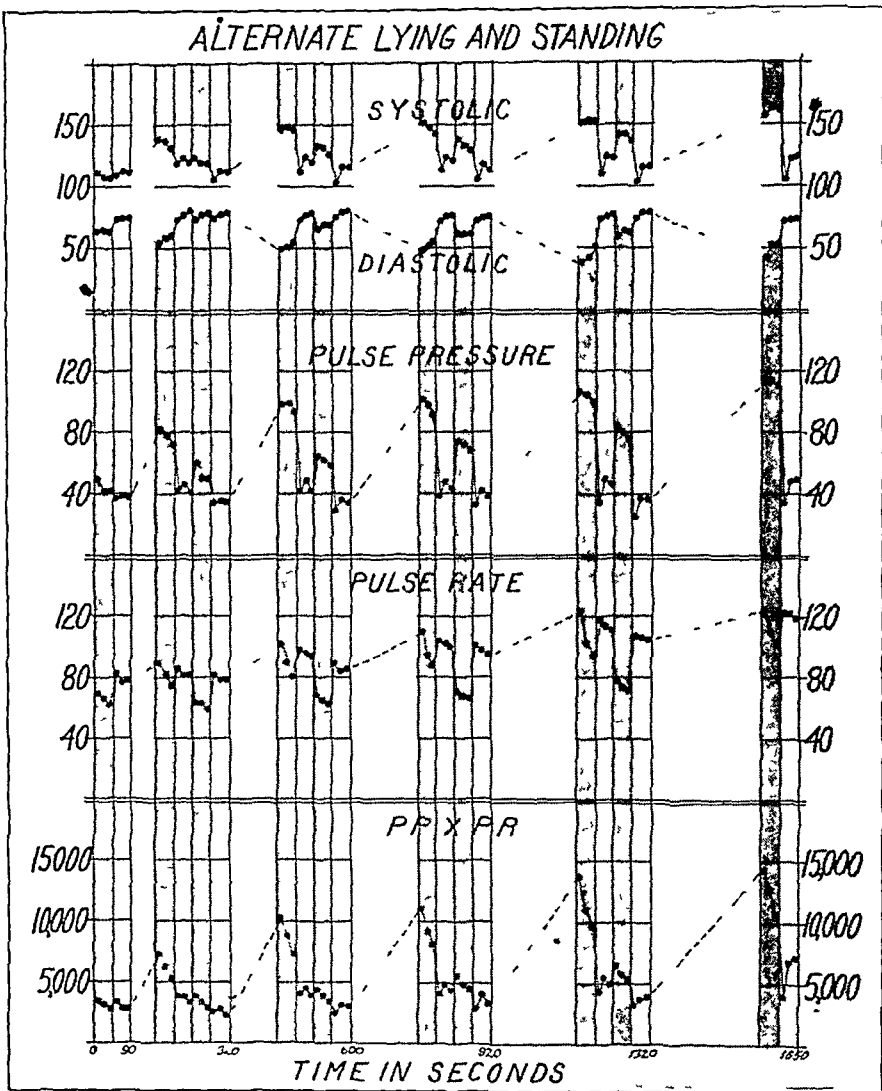


Fig 7—Alternate Lying and Standing Average blood pressure and pulse rate reactions of a group of five normal persons observed while they alternately lay down and stood up during forty-five second periods in the intervals between increasing amounts of exercise The darker areas are the periods when the subjects were lying down, the lighter the periods during which they were standing It will be noted that the $PP \times PR$ curve is almost smooth after 100 hops but that on standing there is a progressively increasing break in the curve as the amount of exercise increases

The foregoing interpretation of changes in blood pressure and pulse rate measurements after exercise in the light of knowledge of the actual circulatory effect may be used as a guide in discussing the effect of change of position, a question in which we have no decisive knowledge

to guide us and one in which we shall accordingly have to depend on pressure and pulse rate observations alone. One result of difference in body position has already been noted in the comparison between readings made in the lying and in the standing positions, but a more striking result was obtained when the subjects were required alternately to lie down and stand up at forty-five second intervals. This experiment was carried out on the same group of five individuals from whom the readings charted in Figures 3 and 4 were obtained. The results are shown in Figure 7. The darker areas in the chart are the periods when the subjects were lying down, the lighter the time during which they were standing.

The general result of these sudden alterations of position is that the smooth curves obtained in the experiments in which one position was continuously maintained are replaced by broken curves. The breaks recur regularly at each change of position. On standing, the systolic pressure drops and the diastolic pressure rises, so that there is

TABLE 8—EFFECT OF CHANGE OF POSITION. COMPARISON OF OBSERVATIONS ON SUBJECTS IMMEDIATELY AFTER THEY STOOD UP WITH OBSERVATIONS ON THE SAME SUBJECTS AT THE SAME POINT IN THE EXPERIMENT ON CONTINUED STANDING

Exercise Number of Hops	Position	Blood Pressure		Pulse Pressure	Pulse Rate	P P × P R
		Systolic	Diastolic			
100	Standing after lying	117	73	44	83	3,835
	Standing continuously	133	76	57	94	5,380
200	Standing after lying	111	71	40	97	3,870
	Standing continuously	143	74	69	98	6,736
300	Standing after lying	111	71	40	104	4,160
	Standing continuously	148	65	83	107	8,900
400	Standing after lying	110	73	37	118	4,350
	Standing continuously	140	68	72	114	8,180
500	Standing after lying	105	71	34	123	4,190
	Standing continuously	138	63	75	123	9,548

a great decrease in pulse pressure. But it will be noted that with every change in the pulse pressure curve there is a change in the contrary direction in the pulse rate curve. If these counterbalancing alterations in pulse pressure and pulse rate had exactly neutralized one another the P P × P R curve would have been quite smooth. But as the amount of exercise increases the breaks in the P P × P R curve become more and more marked. After 100 hops the curve is almost smooth, but after 500 hops there is a very pronounced fall during the first fifteen seconds after standing. So far as the product is concerned, these breaks in the curve immediately after standing are all that distinguish this alternate lying and standing experiment from the lying experiment or the standing experiment on the same subjects. In the latter the P P × P R curves are quite smooth, in this one they are broken. It is evident that in this experiment during the period immedi-

ately following the assumption of the erect position, and during this short period alone, some new factor becomes operative which has the effect of diminishing the $P \times P \times R$ product. Elsewhere the product is smooth, and the changes in pulse pressure and pulse rate are such as have already been noted as characteristic of the standing as opposed to the lying position, and leave the $P \times P \times R$ unaffected. But in this first fifteen seconds after standing something happens which is not present when the erect position is continuously maintained. This is evident from Table 8 in which the readings made during the first fifteen seconds after standing in the alternate lying and standing experiments are contrasted with readings made during the same period in the continued standing experiment.

In the figures from the continued standing experiment the $P \times P \times R$ product increases from 5,380 after 100 hops to 9,548 after 500 hops. The increase after each increment of exercise is, it is true, not so uniform as in the experiments in which the lying position was maintained, but there is, nevertheless, evidence of a relation between the amount of work done and the magnitude of the product. But in the alternate lying and standing experiment the product at this period is only 3,835 after 100 hops and after 500 hops it is only 4,190, that is to say, the product is not only considerably lower throughout, but fails to show the increase on additional exercise which occurs in all the other experiments.

The correspondence we noted between changes in the $P \times P \times R$ product and known changes in volume flow of blood allow us to interpret these abnormally low products as indicative of a failure of the cardiovascular system to supply the large amount of blood required on account of the amount of muscular work performed. We may, therefore, conclude that after exercise the sudden assumption of the erect position is associated with a transitory circulatory failure. The mechanism of the inadequate blood supply, however, cannot be deduced from the product alone but must be looked for in the pressure and pulse rate changes from which the low products are derived. Table 8 shows that in the alternate lying and standing experiment the pulse rate is essentially the same as in the continued standing experiment, so we may conclude that the circulatory failure is not due to an insufficient number of systoles of the heart. After 500 hops when the circulation rate is most defective, the pulse rate is exactly the same as in the continued standing experiment, and it is clear that at this and at all other points the product is low because of the low pulse pressure. After 500 hops, for instance, the pulse pressure is only 34 as against 75 on continued standing. We may, therefore, conclude that the circulatory failure is due to an insufficient systolic output at each contraction of the heart. Figure 7 shows how great is the drop in pulse pressure

towards the end of the alternate lying and standing experiment and also how rapidly the discrepancy is made good. We must, therefore, seek an explanation for an inadequacy in systolic output per beat occurring during the first fifteen seconds after the assumption of the erect position in normal individuals fatigued by exercise.

Cardiac inhibition will not explain it for the pulse rate quickens. It cannot arise from cardiac failure because the output increases again almost at once. It can then only be due to a temporary decrease in the amount of blood flowing back to the heart, and the blood which failed to return to the heart must have been held in the capillaries or in the veins. The low systolic pressure is sufficient evidence that it was not in the arteries. But why should a pooling of blood in the capillaries or in the veins occur, as Figure 7 shows it does, only when the subjects changed from the lying to the standing position? A purely mechanical answer would be that in the erect position the blood from the greater part of the body—the abdomen and limbs—has more difficulty in getting back to the heart because it has to run up hill against the force of gravity. But the differences shown in Table 8 between the alternate lying and standing results and those obtained in the continued standing experiment cannot be accounted for in this way, because at the period chosen for the comparison the force of gravity was equally operative in both experiments. The effect of gravity may, nevertheless, be an adequate explanation of the differences in the pulse pressure and pulse rate levels in Tables 6 and 7, and in Figures 3 and 5, as compared with Figures 4 and 6. In these experiments the only essential difference in the conditions was that in the lying position the force of gravity was in abeyance while in the standing position it was at work. We may conclude, therefore, that the lower pulse pressures and the higher pulse rates observed in the standing position are due to the action of gravity, and they may be interpreted as indicating smaller systolic outputs at each beat of the heart with a larger number of systoles. It is allowable to surmise that this result is brought about by a lowering of pressure in the large veins due to a diminution of the force of the stream of blood returning to the heart when it has to flow uphill against gravity. This decrease in venous pressure would be followed by a decrease in the filling of the heart during diastole, and so to smaller systolic outputs per beat. The increased pulse rate is a compensatory process, designed to counteract the necessary fall in venous pressure and to prevent any decrease in the volume flow of blood.

Another secondary manifestation of the effect of gravity is the "delayed rise in systolic pressure" which is seen only in the standing experiments (Figs 4 and 6). This is surely mainly an effect of

gravity and not as has sometimes been supposed⁸ a result of cardiac weakness. Nor is a temporary pooling of blood in the vessels of muscles suddenly relaxed by the cessation of exercise—a suggestion offered by Cotton, Rapport and Lewis⁹—an entirely satisfactory explanation, for there is no delay in the systolic rise after exercise in the lying experiments in which muscular relaxation must have been more complete than in the standing position. It may be accounted for as the result of a relatively smaller output per beat immediately after exercise due to the combined effect on the venous pressure of gravity and a delayed return of blood held in capillaries dilated by the exercise. As these dilated vessels recover their tone the pressure in the large veins rises, the systolic output per beat increases, and thereby the delayed rise in systolic pressure is produced.

But the force of gravity cannot be the only explanation of the real though transient circulatory failures shown by the breaks in the $P \times P \times P \times R$ curve in Figure 7, because there is no such failure in the continued standing experiments, although the fact that the breaks occur only during the first fifteen seconds after the change to the erect position would appear to show that it is one of the determining factors. But that gravity itself is not enough is indicated in Figure 7 by the fact that the product curve is almost smooth after 100 hops. It is only after 200 hops that a definite break occurs, and as the amount of work increases, the breaks become more and more pronounced so that the amount of muscular exertion which preceded the standing appears to have been a contributing factor in causing the delay in the return of blood to the heart. It should be remembered that the amount of work entailed in these exercises was very considerable, and although the subjects chosen were strong and healthy, they showed very evident signs of fatigue before the end of each experiment. Another proof that fatigue is a necessary factor is the absence of any break in the $P \times P \times P \times R$ curve shown in Figure 1 which was obtained from 300 normal subjects after 100 hops.

Why should a transient decrease in the return of blood to the heart occur when normal individuals, who are tired with muscular work, stand up? The phenomenon suggests a temporary failure under fatigue of some regulatory mechanism concerned with the adaption of the circulation to withstand the force of gravity. Krogh's¹⁰ demonstration of the power for active contraction possessed by capillaries, and Hooker's¹¹ proof that the capacity of the capillaries and venules is controlled through the central nervous system make it seem not

8 Barringer and Teschner *Arch Int Med* **16** 795 (Dec.) 1915

9 Cotton, Rapport and Lewis *Heart* **6** 269, 1916

10 Krogh *J Physiol* **53** 399 1920

11 Hooker *Am J Physiol* **54** 30, 1920

unlikely that the blood which failed to return to the heart in our experiments may have been held in the capillaries and venules because under the influence of fatigue the central nervous system did not induce so quickly as usual the constriction of these vessels which would have prevented any pooling of blood within them under the influence of gravity

The circulatory abnormalities shown in Figure 7 can be explained under the terms of this hypothesis. They arise under conditions of fatigue from muscular exertion as the result of a failure in the central nervous system. The failure consists in an inability to produce with sufficient promptitude the increase in the tone of the capillaries which is required to meet the effect of the force of gravity on the blood when the erect position is suddenly assumed. As a consequence the capillaries dilate before the strain, the blood is pooled in the tissues, there is a marked fall in venous pressure, in diastolic filling of the heart, and so in systolic output per beat and in pulse pressure. The systolic pressure falls because of the relatively small amount of blood forced into the aorta. The diastolic pressure rises because of the increased peripheral resistance caused largely by the banked up blood in the tissues. The delay in the return of blood to the heart is not entirely counteracted by the compensatory increase in pulse rate, and the heart for the moment fails to send an adequate supply of blood through the aorta to the body. These transitory circulatory failures are marked by the breaks in the P P X P R curve in Figure 7.

Finally, it may be well to meet an objection which may be raised on general grounds. The reaction of the cardiovascular system to exercise is so smoothly and faultlessly accomplished that it may seem improbable that there can be any failure to meet the mechanically much smaller strain involved in overcoming the force of gravity. But the perfection of the adaption to exercise is the fruit of uncounted ages of evolution. The adaption to the erect position is only recent and is not yet complete.

SECTION III

PRESSURE AND PULSE RATE REACTIONS IN PATIENTS

1 *Irritable Heart*—The normal standards given in the first section of this paper were used in grading the reactions of men suffering from the condition known as irritable heart. A characteristic type of deviation from normality was constantly found. But the degree of deviation in any given patient varied somewhat from day to day or even from hour to hour, and in order to diminish this variability the average of five tests on different days was usually taken. A large number of records were thus obtained from these patients in the routine work of attempting to determine their capacity for military

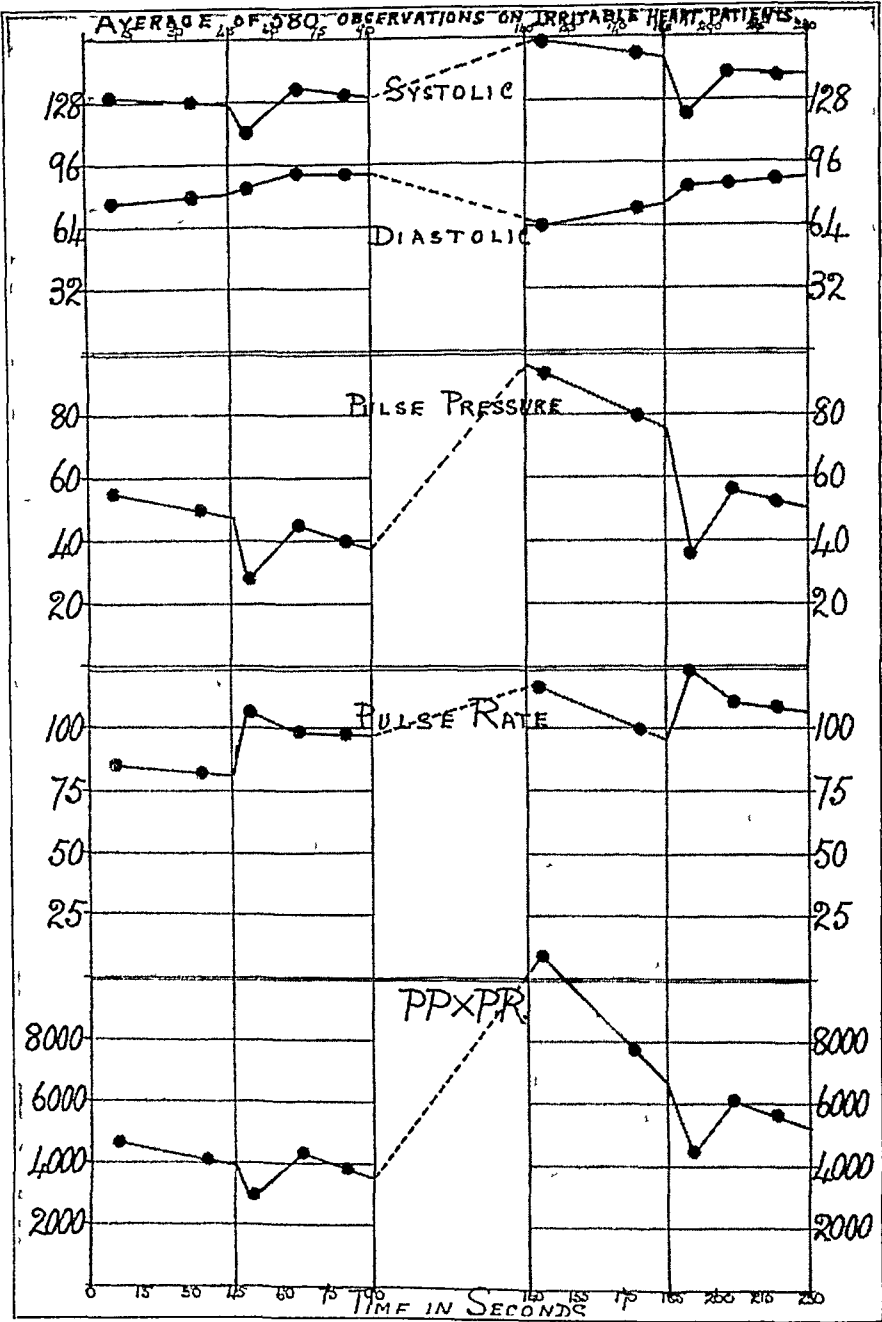


Fig 8—Irritable Heart Patients Average blood pressure and pulse rate reactions derived from 580 observations on 156 cases of irritable heart It will be noted that the breaks in the PP \times PR curve on standing before and after exercise are similar to the breaks in the product curve in normal persons after they are exhausted by exercise (Fig 7), for in both cases these breaks are mainly due to a drop in systolic pressure Compare with Figure 1

service The averages of 580 tests on 156 patients who had been classified as belonging to what has been called the constitutional division of the irritable heart group are given in Table 9 and charted in Figure 8

In these patients the basal and daytime levels of pressure and pulse rate have already been shown to coincide fairly closely with the normal¹² Yet in spite of this essential normality in initial level a comparison of Figure 8 with the curve of the average normal reactions in Figure 1 demonstrates a marked departure from the normal It is therefore a latent abnormality which becomes apparent only under strain

Further, it is an abnormality which is revealed only by a specific type of circulatory strain, i.e., the strain involved in the adaption required when the erect position is assumed Figure 8 shows that the average reaction to exercise is entirely normal The variability is somewhat greater and in some cases there was what we called

TABLE 9—AVERAGE BLOOD PRESSURE AND PULSE RATE OBTAINED FROM 580 OBSERVATIONS OF 156 PATIENTS WITH CONSTITUTIONAL NEUROCIRCULATORY DISABILITY

	Time in Seconds													
	0	15	30	45	60	75	90	140	155	170	185	200	215	230
	Lying			Standing			Hop ping	Lying			Standing			
Systolic	131		129	113	135	131		158		152	121	142	140	
Diastolic	76		79	84	90	91		65		73	84	86	88	
Pulse pressure	55		50	28	45	40		93		79	36	56	52	
Pulse rate	85		82	107	96	95		116		99	123	110	108	
P P × P R	4680		4120	2990	4320	3800		10788		7750	4440	6160	5620	

“overaction”, i.e., an excessive increase in the P P × P R product after exercise, but on the average these patients have an adequate and normal response to the strain of exercise On the other hand, the average curves show a pronounced deviation from the normal immediately after standing both before and after exercise In some individual cases the difference from the normal was slight, in others, it was very marked and constant And, in general, there seemed to be a fairly close relation between the severity of the symptoms and the degree of difference from the normal

The nature of the abnormality is clearly shown in Figure 8 After standing there is a break in the P P × P R curve where it is almost smooth in normal individuals These breaks are due to a sudden fall in pulse pressure and this again is mainly due to a drop in systolic pressure If Figure 7 is consulted it will be seen that the abnormality

in the patients is in every respect similar to the failure in circulation which occurs in normal individuals when they are required to stand up after being tired with a considerable amount of muscular work. The only difference between the patients and the normals consists in the fact that this failure appears in the patients before they have done any work at all, while in normal individuals some degree of exhaustion by muscular exertion is required before any failure can be demonstrated.

The cause of this particular form of circulatory failure has already been discussed in Section II. The conclusion was reached that the immediate cause is a failure of the capillaries to affect the adjustment of capacity required to counterbalance the force of gravity when the vertical position is assumed, and that the primary cause is a failure of the complex coordination of impulses which is required of the central nervous system. This explanation, which is in accordance with the facts observed in normal persons, is also in harmony with the signs and symptoms observed in the patients. As their hands hang down

TABLE 10—BLOOD PRESSURE AND PULSE RATE REACTIONS IN A PATIENT WITH HYPERTENSION AND SYMPTOMS SUGGESTIVE OF CARDIAC WEAKNESS

	Lying			Standing			Hopping 25 Times	Lying			Standing		
Systolic	220	210	215	205	210	205		200	210	210	220	210	210
Diastolic	150	160	150	150	155	145		135	145	150	150	155	155
Pulse pressure	70	50	65	55	55	60		65	65	60	70	65	65
Pulse rate	104	100	104	104	100	100		108	104	104	108	100	92
P P P R	7280	5000	6700	5720	5500	6000		7020	6760	6240	7560	6500	5980

they are engorged, cyanosed and cold. This is the visible evidence of the delay and accumulation of blood in their capillaries. As they rise from the recumbent position, they become dizzy and faint. This is evidence of a failure in the return of blood to the heart and consequent temporary cerebral anemia. Their palpitations, precordial pain, and dyspnea, when conditions call for a sudden increase in the volume flow of blood, are the result of an inadequate and irregular return flow of blood to the heart from their dilated capillary areas. And there was ample clinical evidence in these patients of the nervous instability which I believe is at the root of the condition. A neuro-pathic family history is almost constant in the constitutional type, and a great variety of symptoms could be traced ultimately to defective nervous control. Later as men began to return from France many were seen who presented the same symptoms found in the constitutional type, though in less marked degree. They showed the same pressure and pulse rate reactions, though the fall in pulse pressure on standing was less pronounced. Psychic or physical exhaustion seemed to be the cause in this group of acquired cases and in them

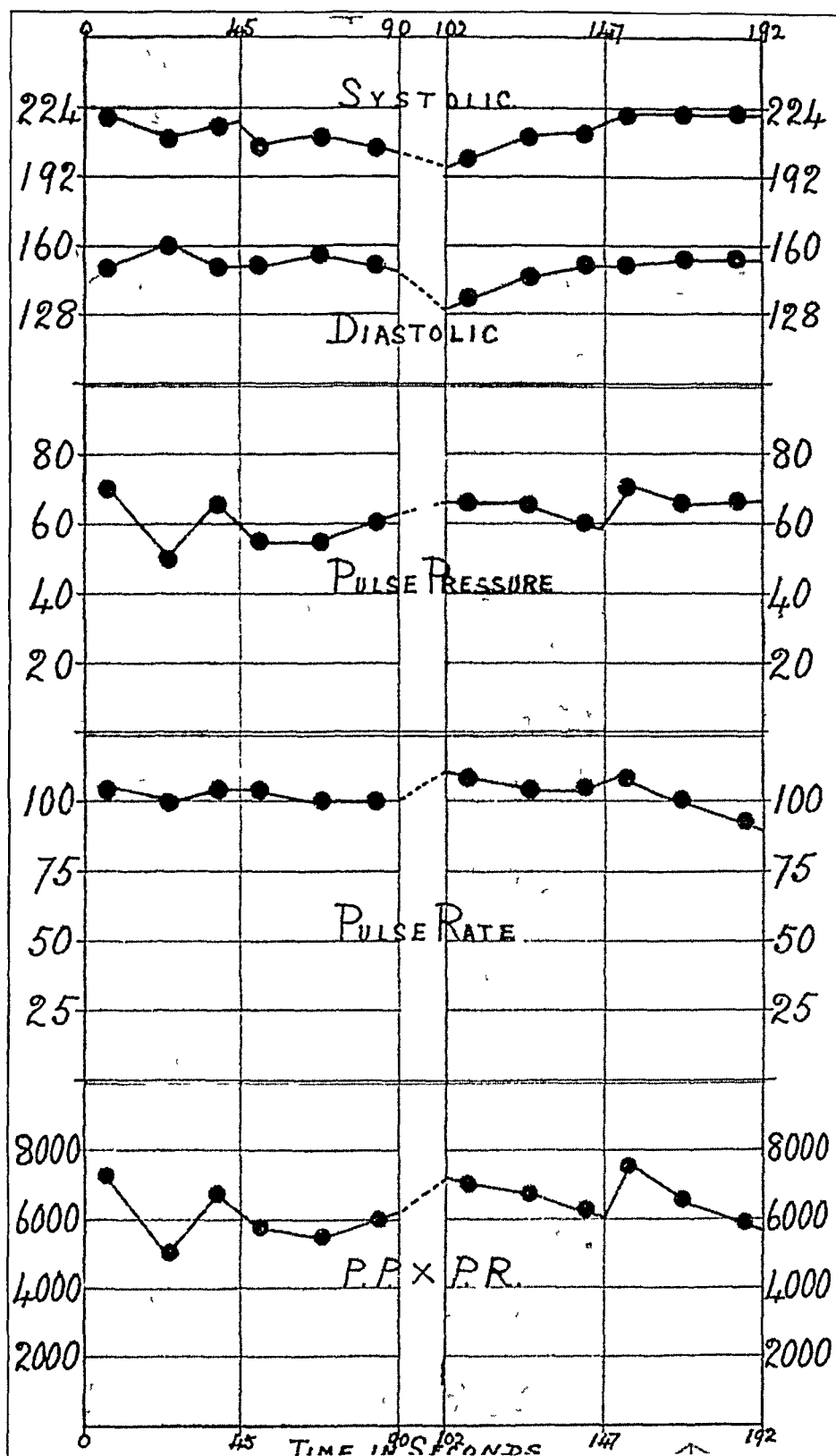


Fig 9—Cardiac Failure The blood pressure and pulse rate reaction of a patient who showed evidence of an early stage of cardiac decompensation

TABLE 11—FREQUENCY DISTRIBUTIONS OF PRESSURE AND PULSE RATE OF 300
NORMAL INDIVIDUALS

	Time in Seconds														
	0	15	30	45	60	75	90	140	155	170	185	200	215	230	
	Lying			Standing			Hop ping	Lying			Standing				
Systolic Pres sure															
81- 90	7	6	6	2	1	2		1	2	2					
91-100	18	17	19	22	6	11		2	2	2		4	2	4	
101-110	32	33	30	45	23	24		2	4	7		18	8	11	
111-120	65	76	78	82	54	61		8	13	25		37	27	30	
121-130	83	73	75	66	73	82		26	34	40		65	47	69	
131-140	47	53	50	45	72	62		50	45	54		71	72	62	
141-150	31	25	28	19	31	29		46	55	56		48	56	59	
151-160	12	11	4	13	18	19		56	56	47		28	32	30	
161-170	9	3	3	3	10	6		49	53	42		16	34	19	
171-180	3	3	1	2	8	3		36	20	13		8	11	7	
181-190				1	2	0		13	8	5		5	7	6	
191-200					2	1		8	4	4			3	3	
201-210								1	3	3			0		
211-220								2	1				1		
Diastolic Pres sure															
31- 40								1							
41- 50								27				1			
51- 60	5	3						82	46	24		20	7	4	
61- 70	84	65	61	35	21	13		105	106	86		41	31	31	
71- 80	103	110	110	84	58	57		48	85	105		107	88	84	
81- 90	69	77	80	99	113	113		32	39	61		79	101	98	
91-100	16	26	32	54	70	70		5	13	18		39	48	53	
101-110	4	3	5	19	24	29			3	4		12	20	24	
111-120		1		2	9	13						1	4	6	
121-130					1	1							1		
Pulse Pressure															
11- 20	2	5	5	20	2	6		1	1	1				2	
21- 30	28	29	41	74	45	73		1	1	3		20	7	14	
31- 40	70	86	93	105	101	110		0	5	11		46	34	49	
41- 50	99	106	101	67	96	75		6	9	30		73	71	85	
51- 60	61	48	43	25	37	26		14	35	58		81	83	84	
61- 70	20	15	13	9	11	9		41	59	77		39	60	39	
71- 80	12	8	2		5	1		60	71	60		23	26	16	
81- 90	8	3	2		1			59	59	32		12	13	9	
91-100					2			66	42	22		5	3	2	
101-110								31	13	4		1	3		
111-120								16	4	1					
121-130								4	0	1					
131-140								0							
141-150								0							
151-160								1							
Pulse Rate															
45- 52		5	8	1	3	4									
53- 60	14	26	33	2	7	10				5		5		6	
61- 68	38	67	77	7	31	36		3	13	17		1	9	14	
69- 76	80	85	84	35	70	79		10	43	64		18	30	36	
73- 84	78	53	43	51	75	69		39	61	74		23	39	46	
81- 92	43	40	36	78	53	42		47	71	71		56	66	60	
89-100	34	11	12	54	18	20		75	62	38		60	54	52	
97-108	8	8	7	37	23	21		39	22	18		59	48	41	
105-116	2	2		17	10	15		48	21	8		43	21	21	
113-124	2			12	8			16	4	3		15	15	14	
121-132	1			5	2			18	2	2		20	10	9	
129-140				1				1				4	3	1	
137-148								3	1			1			
145-156								1							
P P × P R															
1000- 1999	17	25	37	17	15	20		1	1	1					
2000- 2999	53	75	85	86	78	109		2	3	8		16	1	4	
3000- 3999	93	99	107	84	95	97		2	8	28		32	15	18	
4000- 4999	58	58	37	69	61	40		6	23	50		72	35	63	
5000- 5999	47	25	25	34	29	28		19	51	72		72	70	75	
6000- 6999	13	13	7	6	13	6		34	71	53		73	67	63	
7000- 7999	12	3	1	1	6	1		52	44	40		43	52	38	
8000- 8999	6	1	0	2	2			42	32	28		32	28	23	
9000- 9999	0	1	1	0	1			42	32	28		15	17	8	
10000-10999	0			0				38	36	13		10	5	6	
11000-11999	1			0				33	22	7		7	8	1	
12000-12999				1				35	7				2	1	
13000-13999								15							
14000-14999								11							
15000-15999								9							
16000-16999								0							
								1							

the nervous element was strongly marked. The condition is also common as a temporary sequel to all varieties of acute infection, and the same type of abnormality in pressure and pulse rate reactions is found. I believe that the same cause is at work in these three groups of cases. But we have no satisfactory term to describe the condition. Irritable heart is unsuitable because the heart itself is not at fault. Effort syndrome is not entirely satisfactory because muscular effort is not essential for the production of the symptoms. Neurocirculatory asthenia does not quite fit because weakness is no necessary part of the picture. The term neurocapillary stasis is suggested because it calls attention to the mechanism which causes the syndrome.

Cardiac Disability—The records in cases of compensated valvular defects show no abnormality apart from the well known effects of aortic insufficiency on the diastolic pressure. In definitely decompensated cases the test is inapplicable. But in a few patients who showed evidence of an early stage of decompensation interesting records have been obtained. In Table 10 and Fig 9 are given the pressure and pulse rate of a man, age 44, with chronic diffuse nephritis and a moderate degree of impairment of renal function who was beginning to complain of dyspnea on exertion and occasionally a little edema around the ankles. The heart was enlarged but no evidence of dilation was found.

The striking point about this record is its uniformity, which results from the absence of any appreciable change in pressure and pulse rate after exercise. This was not due to an insufficient amount of exercise. The number of hops had to be restricted because of the patient's dyspnea. It suggests, rather, the forced uniformity which would result if the heart, before the exercise, were already doing all it could. It resembles the phenomenon seen in renal decompensation where a constant rate of excretion is maintained under conditions which induce great variation in normal persons.

SUMMARY

SECTION I

1 Blood pressure and pulse rate curves showing the effect of exercise and of change of position were obtained from 300 normal persons.

2 It was found that the degree of change in pressure and pulse rate produced by exercise and change of position is in part dependent on the level of pressure and pulse rate existing before the exercise or change of position. This fact must be taken into account in computing standards of normality. A separate standard for each initial level must be established.

3 Averages and standard deviations for pressure and pulse rate reactions to exercise and change of position are given for a series of initial levels

SECTION II

1 Blood pressure and pulse rate observations on normal persons before and after progressively increasing amounts of muscular work were charted as curves and examined with a view to finding whether it was possible to derive from them any indication of the regular increase in the volume of blood flow which is known to occur after each increase in muscular exertion. It was found that the systolic and diastolic pressure curve showed no constant relation to the work, and that the degree of increase in the curves of pulse pressure and pulse rate varied not only with the work but also with the position of the body. The only curves which under all conditions corresponded to changes in volume flow of blood were the curves derived from the $PP \times PR$ product.

2 When normal persons were tired by muscular work, and were required to change from the recumbent to the erect position, there was an immediate, though transient, decrease in the $PP \times PR$ product curve. The correspondence between changes in volume flow of blood and changes in the magnitude of the product, the nature of the pressure changes which gave rise to the decrease in the product, and recent evidence as to the contractility and innervation of the capillaries, are taken as a basis for the hypothesis that the product changes indicate a failure of the circulation to meet the effect of the force of gravity. The circulatory failure is secondary to a failure of the central nervous system to produce with sufficient promptitude the increased tone of the capillaries and venules which is necessary in order to prevent an accumulation of blood in the tissues when the erect position is assumed.

SECTION III

1 The type of abnormality in pressure and pulse rate reactions and the signs and symptoms found in patients suffering from the irritable heart syndrome support the hypothesis that the cause of the condition is a failure of nervous control over the capillaries.

2 It is suggested that when weakness of the heart is the primary cause of circulatory failure the pressure and pulse rate curves show an unusual degree of uniformity in level before and after exercise. This uniformity results from an absence of the increase in pulse pressure and pulse rate after exercise which is one of the manifestations of that increase in volume flow of blood with which the normal heart meets the requirements of muscular exertion.

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INTERPRETATIONS OF THE INITIAL PHASES OF THE ELECTROCARDIOGRAM WITH SPECIAL REFER- ENCE TO THE THEORY OF "LIMITED POTENTIAL DIFFERENCES" †

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LONDON

The subject chosen for this lecture is one on which much has been written in recent years, but upon which there is still no complete consensus of opinion. In a review¹ written about three years ago I attempted to explain the constitution of the electrocardiogram on a new basis and put forward views of a novel kind. These views have been accepted by a number of workers, from other workers they have received criticism, publicly or privately expressed. The lack of uniform conclusions, I think, results largely from misunderstandings, such misunderstandings as may be expected to arise when the subject discussed is not only intricate but concerned with the ultimate processes of cellular activity and its manifestations. In studying the electrocardiogram we attempt to explain its general deflections in rational terms, yet the terms which we are forced to employ are terms which refer to intimate and intangible effects of cellular physics and chemistry. Although, as may be acknowledged at once, I have experienced recurring difficulty in my attempts clearly to conceive the manner in which the electrical events are related to events in the muscle, yet the conception at which I arrived some few years ago and which is now reconsidered in the light of recent discussion and observation has not altered fundamentally, though it may, perhaps, have grown a little clearer during the interval. In attempting a more distinct statement of the case it seems desirable to state that while I refuse to stand committed, once and for all, to these views, yet our present knowledge does seem to necessitate movement from the older hypotheses in some such direction as will be indicated.

In discussing the question before us one rule stands out as paramount in importance, the facts and the hypotheses must be divided from each

† Seventh Mellon lecture

* Working on behalf of the British Medical Research Council at University College Hospital Medical School, London. Delivered before the Society for Biological Research, School of Medicine, University of Pittsburgh, May 8, 1922, and before the California Academy of Medicine, San Francisco, 1922.

¹ Lewis. The Mechanism and Graphic Registration of the Heart Beat, London, 1920.

other as scrupulously as possible. Hypothesis cannot be avoided, perhaps never will be avoided, in a full consideration of our problem, and it would be presumptuous if my views were brought before you as views approaching to a final solution. Nevertheless, by carefully weighing our present knowledge, certain final statements may be made, certain statements may be denied and we can bring our conceptions a step

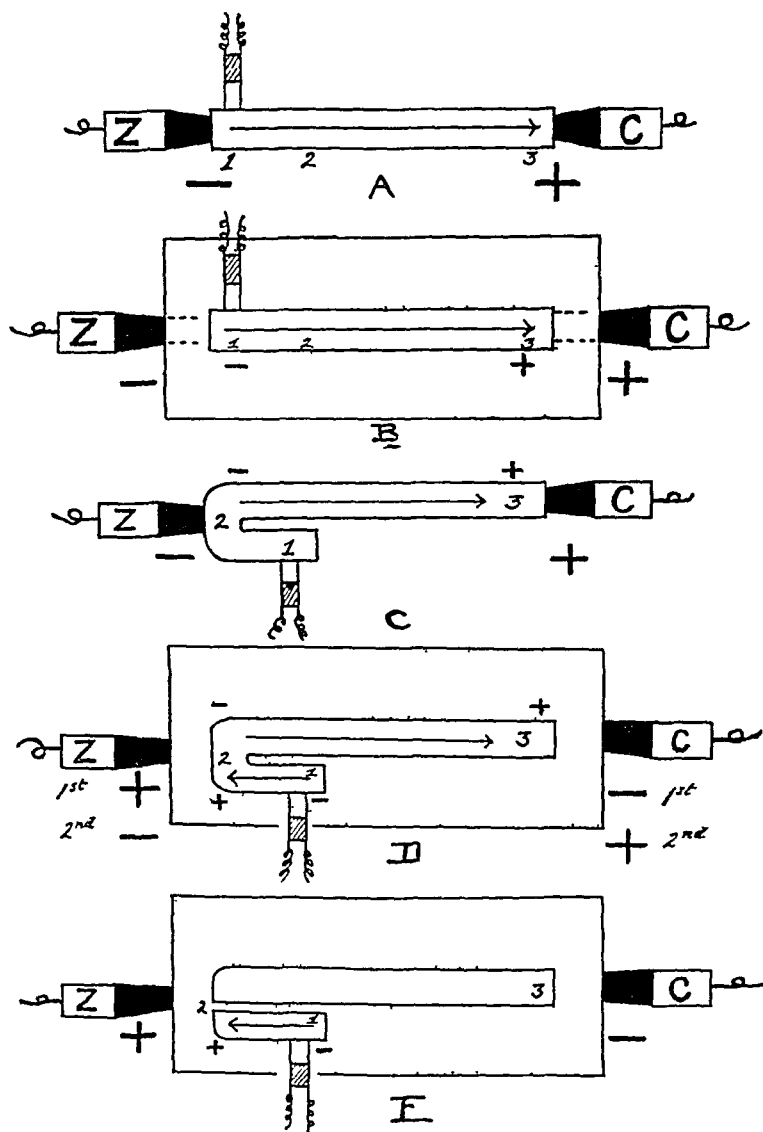


Fig 1—Diagrams, illustrating the potential differences in simple muscle strips activated at one end

nearer clarity and truth. Of one thing I feel sure, namely, that a close consideration of the views expressed, and further observations tending either to support or to destroy them, will prove fruitful.

In considering the meaning of the electrocardiogram, we have all started from a common basis. By common consent, if you place two leading-off electrodes directly on the two ends of a narrow strip of

uninjured muscle (Fig 1 A) and now stimulate the muscle to contract in the region of one contact, the galvanometer shows the development of a difference in potential between the two contacts, that which lies at the point stimulated (*Z*) becoming negative relative to its fellow (*C*). The galvanometer shows us that an electromotive force is developed between these two points, current flows from one to the other through the muscle and through the galvanometer. This experiment, easily performed, has been carried out by very numerous observers with uniform results, the same event is witnessed whether voluntary or cardiac muscle is used, but it is the last only which I shall ask you to hold in mind during this lecture, for it is on cardiac muscle alone that I feel competent to speak, and in respect of which alone I shall draw my conclusions. It is on this experiment that the conclusion, which we have all accepted, is based, namely, that cardiac muscle entering the active state shows relative negativity to muscle which is inactive. But although this observation is easy to confirm, and although the conclusion derived from it does not seem open to question, I believe that it often gives rise to misconception when the meaning of the electrocardiogram is considered in the light of it.

The way in which the chief misconceptions arise I will endeavor to explain ultimately. Meanwhile, it should be remarked that in the simple experiment described the electrodes are placed against very small areas of the muscle strip, this method of leading chiefly signals the events which occur at the ends of the muscle, rather than the events in its whole length. Further, it is to be noted that when a difference of potential arises between the two ends as a result of activity of one end, the current flow is necessarily confined to the line of the muscle, for the muscle is isolated. The line of the muscle represents the line of the electrical axis, or the line of maximal potential difference.

Let us now take a second example (Fig 1 B), one which, in the simple form illustrated, is theoretical, but one which would be more comparable to the experiment of electrocardiography. Imagine a strip of cardiac muscle completely embedded in a moist conducting substance, and that our contacts are placed, not immediately on the ends of the strip, but on the substance in which the muscle lies embedded. So they lie in human electrocardiography. If now the muscle end 1 becomes active, the galvanometer will again record current flow. The muscle end 1 we know becomes relatively negative to the muscle end 3, the contacts *Z* and *C* will no doubt reflect this change. If you wish to do so you may regard the contacts as prolonged through the medium in which the muscle is embedded, to the nearest points of the muscle, *a* *e*, to the original ends 1 and 3. There is this contact, but it is not the sole contact, for our electrodes are now connected, not only to the ends of the muscle, but to its whole surface. This difference

between the two methods of leading off should not influence the direction of the first potential difference exhibited by contact *C* and *Z*, when, as in our illustration, we are dealing with a straight and narrow strip of muscle lying in one line between the contacts, but as we shall see, it becomes of consequence when the relation of muscle to contacts is altered. A second difference between the two methods of leading off is also to be noted. When, in the last experiment, the muscle is embedded in a conducting substance, the current flows not only through the muscle and galvanometer, it flows through the surrounding medium. In other words, we have introduced a series of shunts along the borders of the muscle and these decrease the amount of current flowing through the galvanometer. While we may expect the movement of the galvanometric recorder to maintain its original direction (contact *Z* showing relative negativity to contact *C*), we may not expect its movement to be so considerable.

I emphasize the fact that the comparison made is between an actual experiment (Fig 1 A) and a theoretical experiment (Fig 1 B). The actual events in the second experiment (Fig 1 B) have, I think, not been recorded, though there is sufficient evidence based on observation of a less direct kind to convince us that the curves obtained in the first and second experiment will have the same general form in their initial phase. That there will be this similarity is, I think, generally recognized, it is not a matter in dispute. But this conception is apt to lead up to a second, namely, that curves taken by the two methods are built up in identical fashions and that the two methods of leading will in all circumstances yield similar results. They may do so when a simple and narrow strip of muscle is placed in line with the leading off contacts, but they do not, I believe, in all circumstances. Suppose that the unembedded muscle is bent on itself at one end and that the contacts are placed at 2 and 3 (Fig 1 C). Again, there will be agreement as to the effect produced. Soon after 1 is stimulated, a current will flow through the galvanometer in the original direction, indicating that contact *Z* has become relatively negative to *C*. This change is set up when the muscle on which contact *Z* lies becomes active. It is not produced by activity of the muscle strip between 1 and 2, activity in this portion of the muscle has no material effect since the free end 1 is not connected to the leading off contact *C*. This illustration serves to emphasize the fact that when contacts are placed directly on the muscle, that it is an event occurring in the muscle immediately under the proximal contact which is responsible for the first swing of the recording instrument.

We come next to the fourth and crucial example, the muscle bent on itself and embedded (Fig 1 D). In these circumstances how will the current first flow? I have asked this question of many physiologists

during the past six years, and have obtained almost always the reply that the direction of current flow will be the same as in the last example. It is said that 1 will become negative relative to 3, and that consequently *Z* will show negativity relative to *C*. Now, this reply is an assumption ultimately based on the belief that the two methods of leading off are sufficiently similar, actually the experiment has not been performed in this simple form. For a long while I have felt unable to accept this view of what will happen. The view is inconsistent with certain experiments which will be described presently. The view which I put forward is that relative negativity will first develop at contact *C*, and it will develop at *C* because, when 1 becomes active, we are leading off from the embedded strip of muscle 1 to 2, and the remainder of the strip 2 to 3 does not for the moment concern us. It does concern us of course when the excitation wave in traveling along the strip moves into the region between 2 and 3, when the wave in traveling has turned the corner, *Z* will become relative to *C*, the flow of current becoming in consequence reversed. But for the moment we shall do well to concentrate attention on the first phase of the reaction, for this is in dispute.

The statement just made in respect of the first phase, brings us I think to the critical arguments of the discussion, namely, does the prolongation of the strip from 2 to 3 effect the reaction shown by the galvanometer when 1 becomes active. The usual view has been that it will. My own view is that it does not.

You may ask, why the actual experiment is not performed? The reply is that it cannot be carried out in so simple a fashion on cardiac muscle which is uninjured, and that if you use injured muscle, your experiment is open, on theoretic grounds, to serious criticism. But, as I hope later to show, the experiment can be performed under somewhat more complex conditions, and that it yields the results which I anticipate.

The argument turns as stated on the influence or noninfluence of the portion of muscle 2 to 3, on the initial electrical reaction. According to one view, that which seems so far to have obtained the greater number of direct or indirect supporters, you are to consider 1 as relatively negative, and to consider the whole of the remainder of the muscle as relatively positive. This view implies that in determining the direction of flow, you are to join the center of the active mass of muscle to the center of the inactive mass. According to the other view, you are to consider the part of the muscle which is becoming active as relatively negative, and the inactive muscle in union with it and in its immediate vicinity as relatively positive. I put forward this second view because it is consistent with and explains my experiments and because so far as I am aware it is inconsistent with no other experimental facts, the first view, though it is admittedly consistent with many experiments, is

not consistent with all. For the sake of brevity we may term the first hypothesis that of "distributed potential differences," the second that of "limited potential differences."

At this point it may, perhaps, be appropriate to allude to my previous review. You will perceive that, if the hypothesis of limited potential differences is correct, the direction in which the current sets in the muscle will be the direction in which the excitation wave is at that moment traveling, for it will always move from the point which is becoming active to inactive muscle in the immediate vicinity of the latter. This association, which I believe to be an absolutely constant one,² is one on which I have laid stress, in doing so I have tended to imply that the first is dependent on the second. Such has not been my meaning though it has been inferred from what has been, perhaps, an unfortunate phraseology, and this inference is perhaps chiefly responsible for misconception of my hypothesis. To state that the direction which the excitation wave takes in traveling governs the form of the corresponding curve,³ cannot be considered fundamentally sound.

A more correct expression would be that both are governed by one series of events in the muscle, and in consequence are definitely associated. It has been a matter of descriptive convenience to associate these two phenomena—direction of movement and direction of current flow. But because the meaning may be inferred that one is responsible for the other, I shall endeavor to avoid this method of description in my subsequent remarks.

Returning to the question at issue, namely, the influence of outlying muscle on the electrical reaction, let us consider the case of two entirely separate masses of muscle (Fig 1 E). Under this arrangement, if 1 becomes active, the contacts at C will become negative to the contact Z. Here no one argues that the presence of the inactive muscle strip 2 to 3 will influence the result, it becomes part of the moist substance in which the strip 1 and 2 is embedded. To illustrate this statement, take the example of complete heart block. When the auriculoventricular bundle is divided experimentally or by disease, the electrocardiogram records the independent activities of auricle and ventricle. Each chamber gives its separate curve, but the curves of one and the other fall in

2 I would here express the view that, unless the conditions are very simple, the direction in which the current is setting in a muscle strip as a whole is not to be ascertained with certainty from an examination of two small points of contact on its surface (as in Fig 1 A), but in my view it can be ascertained by the method of leading which Fig 1 B illustrates. When I say that the association between the set of current and direction of travel is constant, I wish to refer to direction of current as ascertained by the method of indirect leading (method of Fig 1 B) and by this method only.

3 The phrase actually used in "The Mechanism and Graphic Registration of the Heart Beat," London 1920.

varying relationship to each other. It is quite clear from such records that activity or inactivity, partial or complete, in one chamber has no influence on the shape or amplitudes of the electrical currents derived from the other (Fig 2). Providing that we are dealing with separate masses of heart muscle, the electromotive forces set up in one chamber are not influenced by those set up in the other. The forces developed in the two chambers find full and individual expression, in explaining such curves we do not balance activity in one chamber against inactivity in the other.

In regard, therefore, to the illustration (Fig 1E) we are safe in assuming that the activation of strip 1 to 2 at point 1 will yield an electromotive force having a certain direction and amplitude, independently of what is happening in the strip 2 to 3. How does this arrangement of the muscle fibers differ from that illustrated by Figure 1D

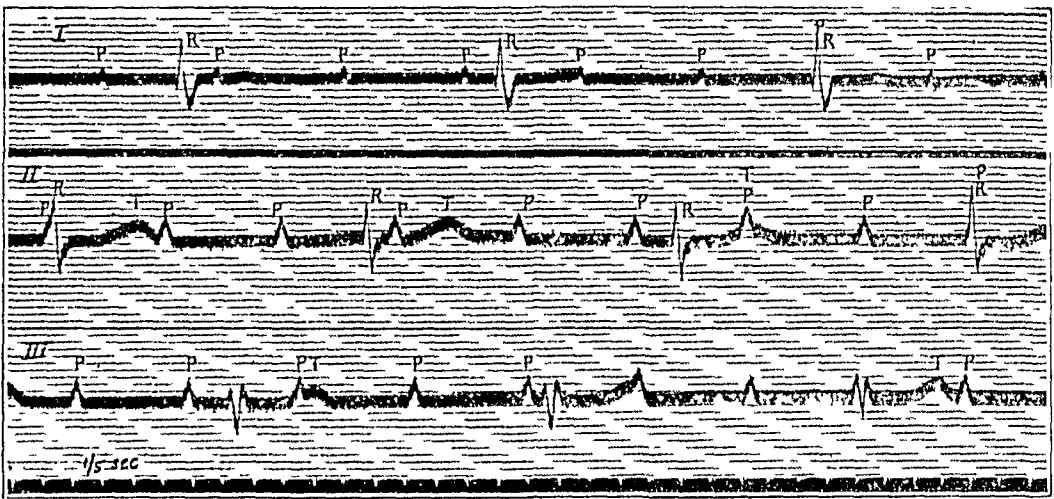


Fig 2 Electrocardiograms from a case of complete heart block, and taken by means of Leads I, II and III

In one respect only, in the first illustration there is functional union between the two strips at the point 2. If 1 is stimulated to activity in these two sets of circumstances, will the initial resultant swings of the galvanometer be in opposite directions, will they indicate relative negativity at *Z* in one case and at *C* in the other? According to the hypothesis of distributed potentials this will happen. But in both instances, when 1 becomes active, the strip 2 to 3 is recognized to be in a state of inactivity. The distribution of potentials is the same in both, unless we are to assume that when the two strips are part of one undivided piece of muscle, an active change happens in strip 2 to 3, rendering it relatively more positive to 1. In other words, if we are to accept the hypothesis of distributed potentials, it is essential to assume that, from its initiation, active change produced by stimulation does not confine itself to that end of the muscle which is stimulated. I know of

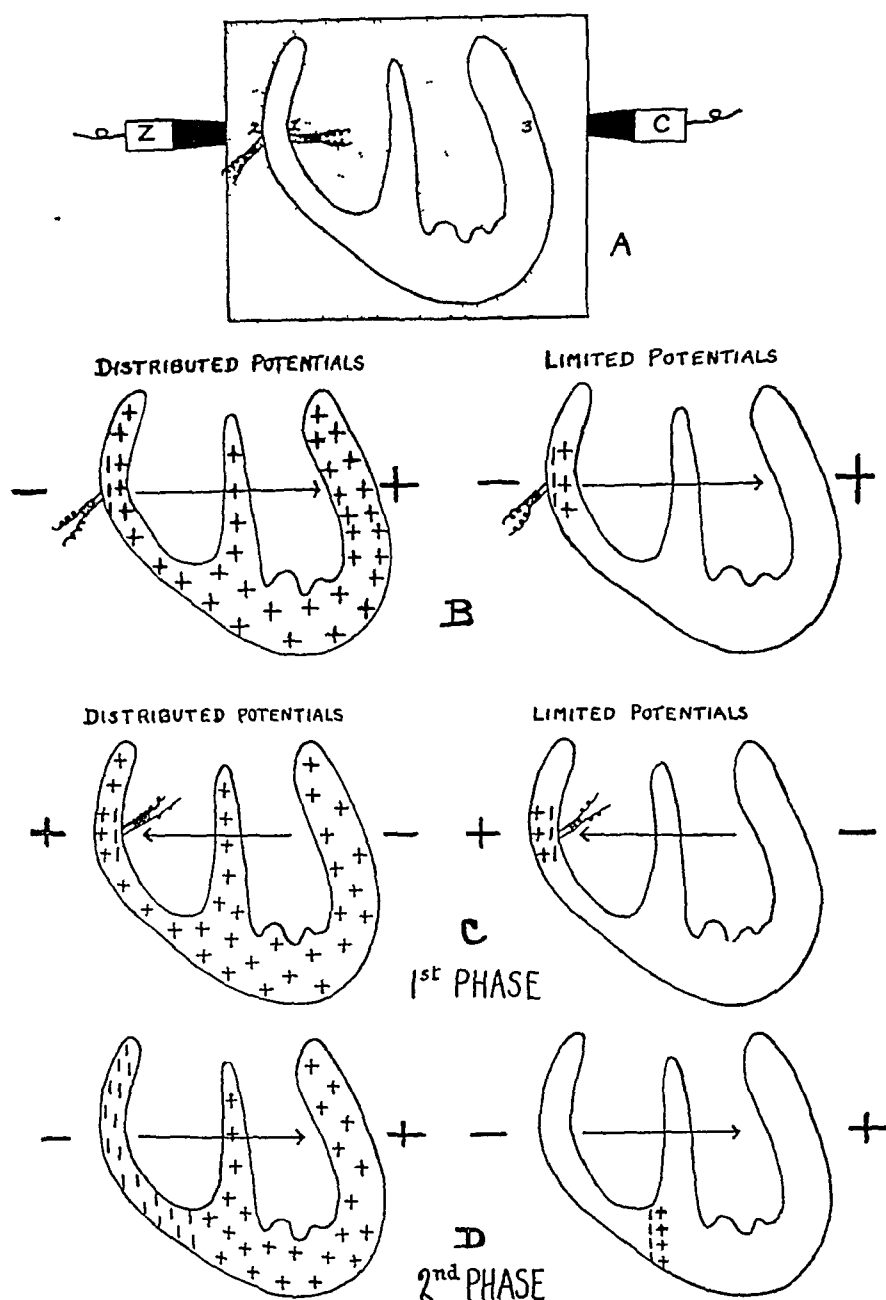


Fig 3 A and B—When the heart is stimulated at its epicardial surface (Fig 3 B), contacts placed in line with the point stimulated show first of all an electrical relation which is indicated by the large + and — signs. This reaction of the contacts is explained alternatively by the hypotheses of distributed and limited potential differences (see small + and — signs of the diagram). In this example the distribution of potentials in the muscle and under the contacts is consistent irrespective of the hypothesis chosen. A, C and D. The heart is stimulated at its endocardial surface and the potential difference recorded by the contacts is at first in one direction (phase 1) and later becomes reversed (phase 2). The supposed potential differences in the muscle, during the second phase, are consistent with what is found at the contact points, irrespective of the hypothesis adopted, but this is not so for the first phase in this the hypothesis of limited potential differences is alone consistent with observation.

no evidence in favor of such a diffused effect, on the contrary, the argument based on the fact that in one instance we are dealing with a single piece of muscle and in the other case with separate pieces of muscle, though plausible, can be shown to be unsound. The experiment of the bent piece of muscle can be performed on uninjured heart muscle. It is accomplished as follows. Leading off contacts are placed on a dog's chest wall (Fig. 3A), the one on the right side, the other on the left, and the right ventricle is stimulated first on its epicardial surface at 2, and secondly on its endocardial surface at 1, the points stimulated being in the same line as the leading off contacts. It will be obvious that, when we stimulate at 2, the excitation wave will move in a general direction in the body from right to left across the heart (from 2 toward 3). It will be equally obvious that if we stimulate at 1 the excitation will at first move in a general direction from 1 toward 2, and that a little later the general course from 2 toward 3 will be pursued. In the

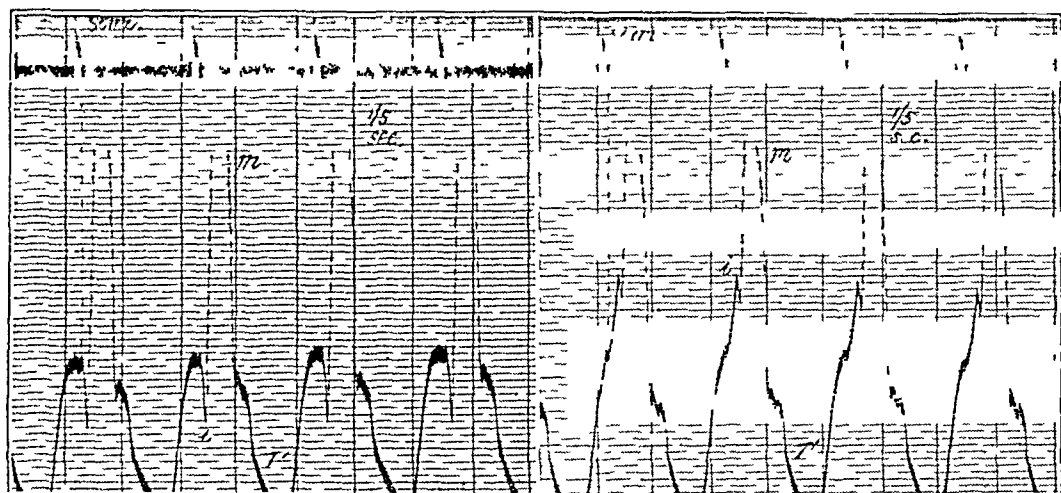


Fig. 4 An example of the findings of four distinct experiments. The lead was from the right chest wall (Z contact) to the left chest wall (C contact) and the wall of the right ventricle was stimulated on its epicardial surface (right hand record), and on its endocardial surface (left hand record). In the last case a small pair of long insulated electrodes was introduced through a small slit in the wall of the conus or through the jugular vein. The two points of stimulation (inside and outside) lay no more than 0.5 cm from each other. The curves differ in one respect, the left hand curve begins with an initial phase i directed downward, in the right hand curve this phase is directed upward. These initial phases of the curves correspond to involvement of the wall at the point stimulated (the involvement being in opposite directions in the two circumstances). The main deflection m is similar in both curves, it represents spread from right to left in the ventricles as a whole. Curves of this kind are obtained most successfully if the lungs are well inflated so that good contact is maintained between the sides of the heart and the chest wall. The curves represent responses to rhythmic break shocks (single shocks give similar effects). The stimulus is recorded electrically in the top line. The curves are not distorted by the stimuli, as the time relations of stimulus and shock show, reversal of the direction in which the stimulus entered the heart did not affect the form of the curves.

first case the general direction in the body will be from right to left throughout the whole excitation of the ventricle, in the second case, it will be for a brief period from left to right, and eventually from right to left. The experiment affords the general condition illustrated by the straight and bent muscle strips of Figure 1B and D. The result of this experiment is instructive. Stimulate the epicardial surface and, from the first, contact *Z* is negative to contact *C*. This finding is consistent with both hypotheses, the potentials being distributed as shown in Figure 3B and in Figure 4. Stimulate the endocardial surface (Fig 3C and D) and the curve has two opposite phases, a short first phase during which contact *C* is negative to contact *Z*, and a longer second phase during which contact *Z* is negative to contact *C* (Fig 4). This finding is consistent with one of our hypothesis only, namely, that of limited potential differences. The association between the set of the current and the direction in which the excitation wave moves will be noted in this illustration. It constitutes a single and new illustration of an association which I believe to be firmly established and of which numerous examples have already been published.⁵ It was because I found this association constantly to exist in the normal heart beat of amphibians, reptiles, birds and mammalia, classes in which the spread of the excitation wave is very diverse, that I first recognized the hypothesis of distributed potentials to be untenable, for it is inconsistent with this association, as the diagrams clearly show (Figs 3C and D).

It may suffice at the present time if a few of the simpler illustrations are cited. The first of these permits the display of some important fallacies. It is the instance of the normal amphibian heart beat. The amphibian heart (Fig 5) comprises not only sinus, auricle and ventricle, but also a bulbus arteriosus. It is on hearts of this or of a closely allied type that almost the whole of the preliminary explanations of the electrocardiogram have been based, and it is with the mistaken interpretation of these curves, and the hypotheses derived from them, that we have today chiefly to contend. In this early work the heart was examined by placing on the base and apex of the ventricle two contacts and connecting them to a galvanometer. Because in such curves as were regarded to be typical, the first deflection indicated relative negativity of the base it was concluded that the base first becomes active, it was further concluded that the excitation wave spreads as a simple wave from base to apex. Now, further and closer observation by modern

4 In stimulating the epicardial surface the curve is not usually expressed as a single phase. It rises a little, hangs or falls away as the endocardial lining is approached, and then rises steeply to yield the chief deflection which represents rapid involvement of a large mass of the ventricular substance.

5 Phil Tr Roy, Soc, B 207 221, 1916

methods has shown that the first of these conclusions is usually incorrect, and that the last conclusion is never true. These early observations on the cold-blooded heart and the conclusions derived from them are open to serious criticism. The direction of the first deflection does not, in point of fact, always indicate primary negativity of the base. The direction depends largely in a given animal on the point chosen at the base for examination, there is also much variation from animal to animal. Later observations have shown that sometimes a basal point is active before the apex, sometimes it becomes active after the apex (Fig 5), sometimes certain points at the base are activated before, and certain points after, the apex. In all cases the base and apex are activated within a very short time interval of each other. The excitation first reaches the surface of the heart at neither base nor apex; it reaches

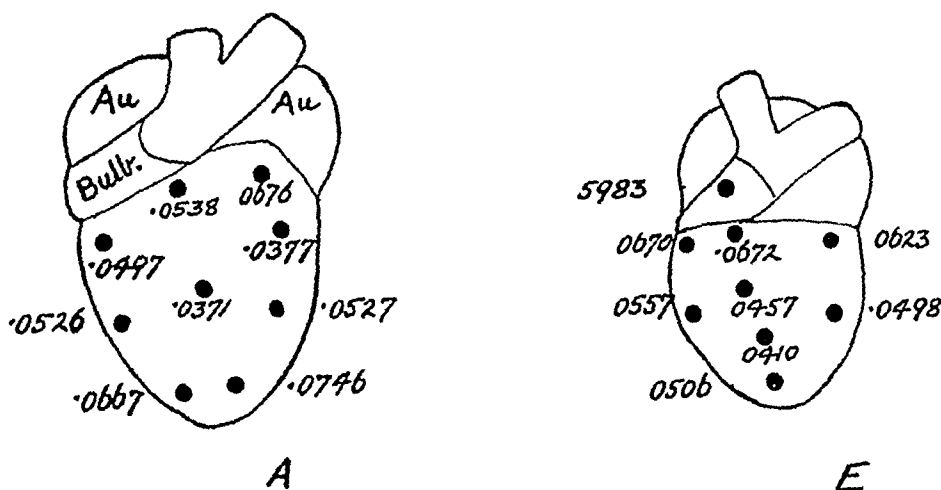


Fig 5 — Outline diagrams of the hearts of *Bufo vulgaris major*, showing a number of surface readings expressed (in decimal points of a second) to the beginning of *R* in an axial lead. Toad A, an unpublished figure, showing that the base is activated earlier than the apex. Toad E (after the original figure) showing that the apex is activated earlier than the base. In both cases the central region of the ventral surface is activated earliest of all. In the axial electrocardiogram of each animal the chief deflection was an upright *R*, in the case of toad E, the electrocardiogram also showed a prominent *S* wave.

the central portions of the ventricle (Figs 5 and 6 A) and races simultaneously up to the base and down to the apex, the race may be won in one other direction, usually it is won at the apex. It is easy to understand why these base-apex curves of early days often seemed to indicate primary negativity of the base. The extreme base does become active a little before the apex in some amphibian hearts, though that is not the rule. If the extreme apex is chosen for one contact, and a point somewhat removed from the base is chosen for the second and this would be the natural tendency⁶ of experiment, primary negativity

6 The tendency being to allow an interval of lesser or greater extent between the contact and the *A-I'* junction.

of the base would usually be manifested, for the reason that a point a little removed from the base is usually activated earlier than a point at the extreme apex. The precise time relations of basal and apical activity being unknown beforehand, this observation would naturally be construed as indicating that the excitation wave starts at the base. From this conclusion, false as it was, it was an easy step to the still very prevalent general erroneous assumption that when, as is the rule, the basal contact of an indirect lead (method of Fig 1 B) first demonstrates negativity, activity is confined to muscle which lies nearer to this basal contact than to the apical one. Thus, in human electrocardiography it has frequently been assumed that *R*, the chief deflection, is essentially a basal effect and that *S* is essentially an apical effect, for *R* represents relative negativity of the basal and *S* of the apical contact. Neither conclusion is justified.

These assumptions, erroneous as I believe them to be, arise chiefly from the idea that if muscle at the base is active, the basal contact will show relative negativity and, conversely, that if the apex is active, the apical contact will show relative negativity. These are views based on the hypothesis of distributed potentials. A primary basal activity may display itself in relative negativity of the apical contact as the experiment illustrated in Figure 3A clearly indicates. The erroneous assumptions also arise, in part, because the base-apex curve of the amphibian, where contacts are laid directly on the heart, has been assumed too rigidly to be comparable with the curves from outlying contacts such as are used in clinical electrocardiography. The difference between the two methods is that in the first the curve chiefly expresses the potential differences between two small areas, one at the base and one at the apex, while in the clinical method the lead (when axial) is from the whole of the basal and the whole of the apical parts of the heart, the clinical curves express the electrical changes in the entire mass of cardiac muscle, the direct leads do not. The two methods are strictly speaking incomparable (compare Figs 1C and D from this point of view).

The axial electrocardiogram of the amphibian heart (Fig 7), in so far as it expresses spread of the excitation wave, consists of the following deflections:

- 1 A chief and primary deflection (*R*) indicating relative negativity of the contact beyond the base.
- 2 An inconstant second deflection (*S*) indicating relative negativity of the contact beyond the apex.
- 3 A deflection (*B*), occurring at a late phase of the electrocardiogram corresponding to activation of the bulbus arteriosus, and indicating relative negativity of the apical contact.

Let us deal briefly with the last deflection first. This bulbus deflection is due to the activity of muscle lying at the base of the ventricle, yet its direction indicates relative negativity of the apical contact. This observation clearly warns us against lightly concluding that relative

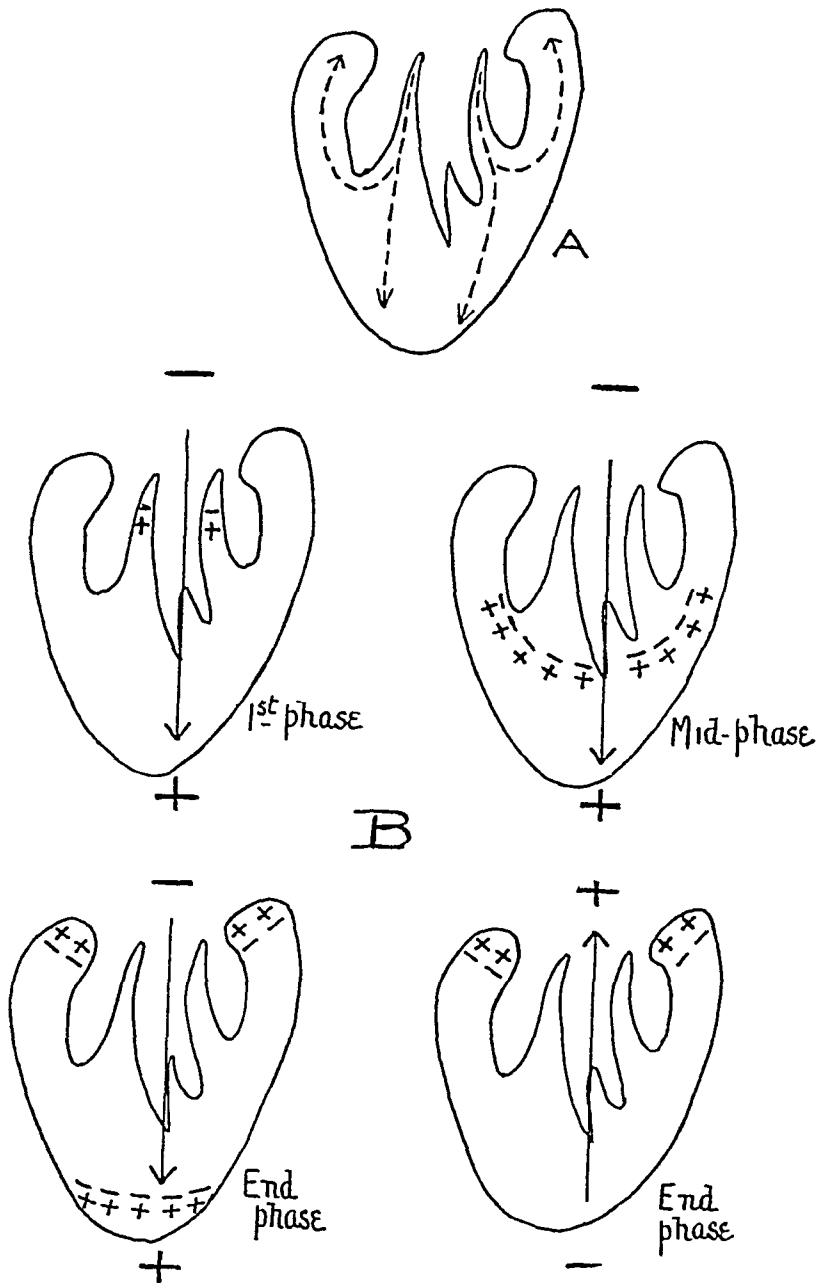


Fig. 6—Course of excitation wave in activation of ventricle

negativity at the apical contact necessarily means activity of the muscle lying nearer to the base than the apex of the ventricle. The direction of this deflection is what it is, because the excitation wave begins in the lower part of the bulbus (1 e, toward the apical contact) and the inactive muscle in its vicinity lies above it (1 e, toward the basal contact).

The position of the bulbus, relative to the rest of the ventricular muscle with which it is in functional union⁷ does not affect the direction of the deflection

Consider now the initial deflection (*R*) or deflections (*R* and *S*) The meaning of *R* according to my hypothesis is not obscure It is due to set of the current in the axis of the heart, *i e* from above downward, over the greater part of that phase of the cycle during which the ventricle is becoming activated The ventricle is activated in the gross from above downward The excitation wave starts in the muscular funnel and trabeculae within the heart (Fig 6A) and is at first propagated wholly in a downward direction Actually the greater part or entire upstroke of *R* is written before the excitation wave appears at any point on the surface of the ventricle To regard *R* as an evidence of general basal activity is obviously inconsistent with this observation, *R* corresponds to the activity of muscle lying deep inside the

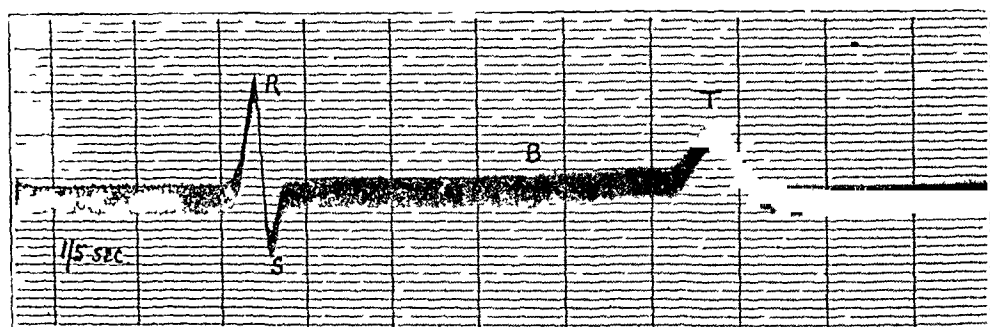


Fig 7—An electrocardiogram taken from a toad's heart, leading from the mouth and abdomen in the axis of the heart The deflection produced by activity of the bulbus arteriosus (*B*) is directed downward

central portions of the heart The hypothesis of limited potential differences applied to the amphibian ventricles provides us with a clear conception of the electrical events, a conception which is consistent with the manner in which the excitation wave has been shown to spread During the early phases of *R*'s inscription the muscle is becoming active in the central trabeculae, this region is relatively negative, the relatively positive region lies apexwards and in its immediate vicinity (Fig 6B 1st phase) As the excitation wave proceeds downward, the advancing border spreads laterally, but the balance of the potential differences manifests itself still in the same direction (Fig 6B midphase) In its

⁷ The reply which has been made, that there is a natural line of block between the two chambers, does not appear to me relevant They are united functionally by muscle fibers, the region of block being simply a region of slow propagation, if it is held that this region of slow propagation constitutes a line of complete separation from the standpoint under consideration, the burden of proving this lies with those who hold the view

further progress the advancing border of the wave is not only proceeding toward the apex, but is now also traveling back in the lateral walls to reach the base (Fig 6 B end-phase left-hand figure). Activity in the region of the apex still tends to maintain the electric axis from base to apex, the basal activity tends to set it in a contrary direction. But the effect of this basal activity is apparently insufficient to upset the average direction, which still remains from base to apex. The basal contact is throughout relatively negative to the apical contact. If, however, as often happens in the amphibian heart, the basal segments of muscle are the last supplied, this opposition of the apical effects is removed and the effect of basal activity then appears. It manifests itself in the form of an S wave, a downward deflection indicating relative negativity of the apical contact. The axis of the electromotive force is now from below upward (Fig 6 B end phase, right-hand figure).

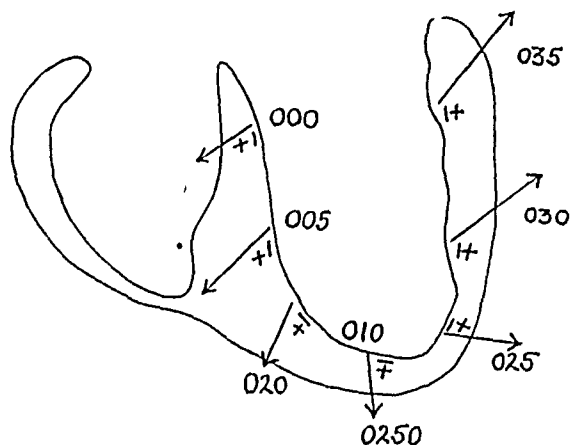


Fig 8—Times of arrival of excitation wave relative to each other indicated in decimal points of a second

Thus, our hypothesis brings us to a reasonable explanation of a curious but actual observation, namely, that the appearance of an S wave in the electrocardiogram of amphibians is associated with late arrival of the excitation wave at the ventricular base. No other present day hypothesis will afford an explanation of this phenomenon. This example is in my view precisely comparable to that of the bulbus already cited. In both instances basal activities are responsible for relative negativity of the apical contact, but the present illustration has an advantage over the first, in that there can be no question here of separate muscle systems, the whole of the musculature of the ventricle is one uniform syncytium.

THE MAMMALIAN ELECTROCARDIOGRAM

Similar methods of observation are applied to the mammalian ventricle and, although in this instance we deal with a far more complex arrangement, similar correlations can be shown to exist between the manner in which the excitation wave spreads and the set of the elec-

trical axis from instant to instant To consider the constitution of this electrocardiogram in full detail would detain us too long, it must suffice if by a single example I illustrate again the general principle of interpretation, and show that the hypothesis of limited potential differences is applicable in this case also Let us take the simpler case, the excitation of the dog's left ventricle

The excitation wave is found by observation to start in the septum of the ventricles, it is traced down the septum to the apex and from the latter up the lateral wall to the base The times of arrival, relative to each other, are indicated in Figure 8 in decimal points of a second But in moving along this semicircular path the wave does not proceed in a direction parallel to the borders of the muscular track, it is penetrating the wall in successive segments of its course, it moves always from within outward along centrifugal paths, each part of the wave travels from the endocardial to the pericardial surface Throughout its passage, the electrical axis constantly changes so that, while in the initial stages this axis sits from left to right in the body, it gradually shifts to a base-apex direction, from this it swings more and more to the left until, eventually, and when the excitation wave is reaching the base of the left ventricle, the electrical axis is directed chiefly upward This change in the direction of the axis is responsible for the complexity of the corresponding electrocardiographic curves When the set of the axis is in the main downward, a basal contact (right shoulder) is relatively negative to an apical contact (left thigh), the corresponding upstroke in the electrocardiogram contributes to the formation of the well-known deflection *R* On the contrary, when the set of the axis is mainly upward, the apical contact becomes relatively negative to the basal contact and the corresponding downstroke in the electrocardiogram is the chief constituent of the well known deflection *S* As in the amphibian heart, *S* does not represent an apical activity, it represents a basal activity Now this example, though complex, is a striking one There is, within the reasonable bounds of error in observation, complete correspondence between the readings which indicate the distribution of the advancing excitation wave and the set of the electrical axis at corresponding phases of the cycle, when the set of this axis is read in terms of my hypothesis of limited potential differences These observations are in full accord with our knowledge of the anatomy of the ventricle, in accord with a distribution of the excitation wave through the left division of the auriculoventricular bundle and its arborization, for the left division enters the ventricle on its septal surface and distributes its branches to the septum, to the apical parts of the heart and to the lateral walls of the heart and to the lateral walls at the base, in this order Consider the ascertained order of spread and arrange theoretic-

cally the electrical axis, using the hypothesis of distributed potential differences, and one arrives at a result which is not consistent with observation. According to this hypothesis, relative negativity should appear, first of all, at the basal contact, secondly when the wave of excitation reaches the apex, the apical contact should appear relatively negative, finally when the wave returns to the base, the basal contact should again show relative negativity. The second and last suppositions are not in accord with the facts. But if, on the other hand, one arranges the potentials theoretically, using the hypothesis of limited potential differences, harmony exists.

In the light of these observations and in the light of those previously described, I have no hesitation in discarding the older hypothesis and in accepting in its place the hypothesis which I term that of limited potential differences. It is in accord, so far as can be seen, with all present observations on heart muscle. I do not claim that it affords a final explanation, being quite prepared to find that future observations will necessitate its modification, but it is desirable, nay it is essential, that we should possess ourselves of an hypothesis which harmonizes with all present day observation, an hypothesis which will serve to direct further experiment along fruitful channels. Hypotheses which are out of harmony with present observations will not serve this purpose. The present hypothesis has been put forward and is now emphasized in the belief that it will supply our present and immediate needs.

A CASE OF HODGKIN'S DISEASE TREATED WITH ROENTGEN RAYS FOR SIX YEARS ¹

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AND
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NEW YORK

INTRODUCTION

Cases of Hodgkin's disease, involving the stomach or wall of the gut, while rare have been reported by various observers (Briquet,¹ Musser,² Wells³ and Reiman⁴) The case reported by Briquet is of interest because it was the first of this type on record, and is accepted now as a case of Hodgkin's disease Apparently in none of the cases referred to was there a perforation of the intestine

Our patient was a young woman observed and treated with roentgen rays for six and a half years Microscopic examinations were made before treatment was instituted, and, again, at the post mortem

The course of the disease, type of temperature ("Ruckfall"), blood findings and many of the physical signs and symptoms are similar to those frequently noted in this disease The case is thought to be of interest for the following reasons

- 1 Length of time the patient was observed and treated with the roentgen ray
- 2 Apparent effect of the roentgen ray on the clinical course and pathology of the glands
- 3 Type of temperature both early and late in the disease
- 4 Termination due to perforation of the intestine

REPORT OF CASE ⁵

Clinical History—F. M. (history No 42181), white woman, aged 22 single, clerk, was first admitted to the Presbyterian Hospital in March, 1914

Chief Complaint—Pain in abdomen and weakness

Family History—Negative

Past History—Swelling of legs was treated by injections (?) three years ago She had had frequent attacks of tonsillitis Her menses were irregular, the last period, one month ago

Present Illness—Nine weeks ago she first noticed a tired feeling, insomnia and anorexia For the past two weeks, she has had a burning pain in the left

* From the Medical Clinic and Pathological Department of the Presbyterian Hospital Columbia University

1 Briquet Cruveilhier's Atlas 2 Pt 34, 1835-1842

2 Musser, J. H. Tr. Assn. Am. Phys. 16 638, 1901

3 Wells, Gideon H. Am. J. M. Sc. 128 837 1904

4 Reiman, S. P. Cleveland M. J. 15 94, 1917

5 This case is one of those referred to by Longcope and McAlpin in their article on Hodgkin's disease in Oxford Medicine

side, radiating to her back. This pain has no relation to meals, but is worse at night. There is no vomiting, epistaxis or swelling of legs. She has lost 15 pounds in weight. Five days ago her temperature was 103 F.

Physical Examination—The patient is a pale thin woman. The tonsils are ragged. The lungs are clear. The heart is negative, except for a soft blowing systolic murmur over the pulmonic area, which is not transmitted.

Abdomen—There is some tenderness on deep pressure one inch to the left of the midline and two inches below the umbilicus. There is no rigidity, no masses or signs of fluid. The liver and spleen are not palpable. Reflexes: Corneal, absent. Others normal.

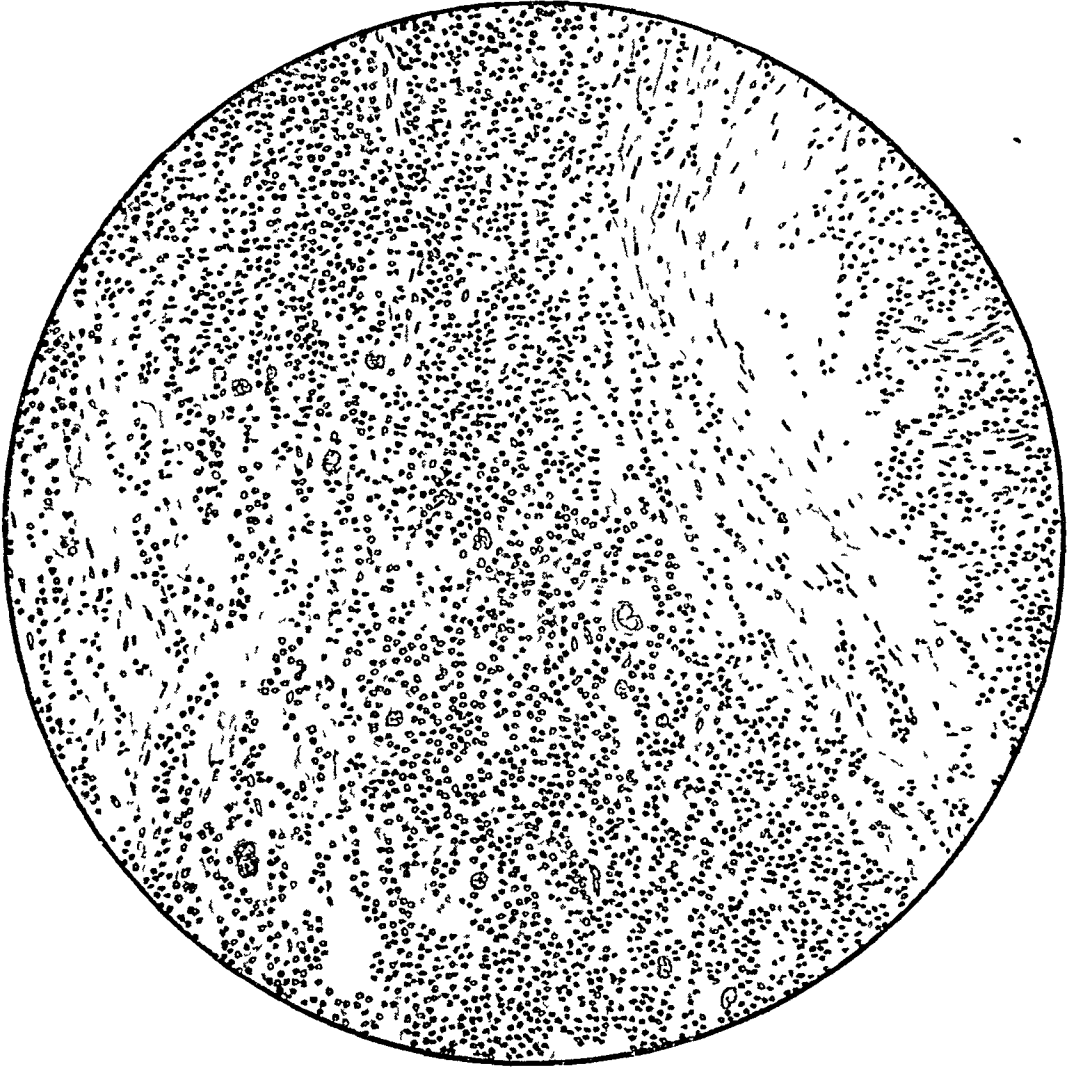


Fig 1—Hodgkin's disease Mesenteric gland

Gastric analysis on two occasions showed a low total acidity, no free hydrochloric acid, no lactic acid, a faint trace of blood. The blood Wassermann and the Pirquet test were negative. Tuberculin and intradermic tuberculin tests were negative. Urine: Negative, except for occasional trace of albumin, no casts.

Clinical Course—Twenty days after admission, a hard, irregular, freely movable mass was felt in the right lower quadrant. It was not tender and there was no rigidity. Percussion over the mass elicited tympanites. Roentgen-ray examination of the abdomen was negative for glands.

Roentgen-ray examination of chest: Throughout the right lung and at apex of the left lung are shadows suggestive of tuberculosis.

The abdominal mass gradually increased in size, and April 18 an exploratory laparotomy was done. There were numerous enlarged glands in the mesentery of the hollow viscera. Some of these measured at least 5 cm in diameter. There were three main masses rather loosely connected and more or less distinct from each other. These were in the mesentery of the ileum and jejunum. The lowest was in the ileocecal angle. The next one lay about over the vertebral column, while the third was well up near the duodenojejunal angle. There were numerous discrete glands beneath and behind the cecum, small nodules, 0.5 cm in diameter, were also scattered in the mesentery. These appeared to be yellowish in color and cheesy.

Pathologic Report (15593)—Mesenteric gland. Gross. Nothing characteristic was noted. Microscopic. Capsule thick and fibrous. Major part of mass consists of lymphoid tissue. Stroma is a fine reticulum. Scattered through this are small round cells and eosinophils, also many cells of the Dorothy Reed type. Evidently, this is a case of Hodgkin's disease, fairly well advanced (Fig. 1).

The wound healed promptly. Later thrombosis of the left internal saphenous vein developed. Pain in the lumbar region was relieved by morphin and paraldehyd. The temperature which had been 101 and 102.8 F, gradually came down. She gained 9 pounds in weight. The mass in the abdomen remained the same. No superficial glands were ever palpable. The heart and lungs were as at the previous examination. Blood pressure was 100/64 and 90/80. Discharged, June 19, 1914.

Interval History—She was admitted to the General Memorial Hospital, July 7, and discharged July 10, 1914. There was tenderness in the epigastrium. A few nodules, size of a hazel nut, were found in the right iliac region, which was the first time that a superficial gland was ever palpated. The spleen and liver were palpable. Roentgen-ray therapy was begun July 24, 1914. Between the first and second treatment one month elapsed. The patient felt better after treatment. Later the roentgen-ray treatments were given every two weeks.

Second Admission—Nov. 14, 1914. Three days before admission she had severe abdominal pain, with vomiting and slight fever. At this time, the general appearance of the patient was improved. A large, hard, nodular mass was felt in the abdomen, extending from the ensiform to the umbilicus, and 3 cm to each side of the midline. It moved with respiration and was slightly tender. No definite mass could be made out in the right lumbar quadrant, but an indefinite sense of resistance was noted. The liver, spleen and kidneys were not felt. Cervical, axillary and inguinal lymph nodes were not palpable. The skin was negative. The eye grounds were normal. Wassermann negative.

Later it was impossible to definitely outline the abdominal mass and most of it seemed to be to the right of the midline. Other smaller masses felt in abdomen.

She had dull aching in the back, radiating about the waist. Temperature gradually rose to 103.2 F. Pain was quite severe and not relieved by fairly large doses of morphin. There followed gradual improvement and the temperature became normal.

Blood cultures (Rosenow deep tubes). Sterile.

Roentgen-Ray Examination (Roentgenogram 31424)—Slight increased diffuse density of lungs. Shadow about roots unusually strong. Left diaphragm slightly irregular with bulging over the spleen.

Discharged, Dec. 22, 1914, somewhat improved.

Interval History—She was given roentgen-ray treatments at somewhat irregular intervals.

March 1, 1915. Deep in both inguinal regions are glands about 2 cm in diameter. None palpable elsewhere. Abdominal mass much smaller and much less distinct.

Sept. 21, 1915. Several enlarged glands in the left supraclavicular fossa formed a mass 6 cm in diameter and about 2 cm thick. These glands decreased

in size under roentgen-ray treatment Abdomen Slight resistance just below costal arch in midline, with indefinite sense of a mass which cannot be mapped out

She has had periods of fever One of these lasted twenty days, and the temperature went as high as 103.2 F

In December, 1916, she showed signs of hyperthyroidism—nervousness, diarrhea, insomnia, palpitation and tremor, but no exophthalmos These symptoms gradually improved during the next two years Roentgen-ray treatment of glands was continued during this period

June, 1918 Menses irregular, some loss of weight, temperature elevated two or three degrees each night Abdomen is somewhat distended, sense of mass made out along median abdominal line Spleen not palpable Some retrosternal dulness Right femoral nodes enlarged

Jan 31, 1919 Abdomen a little full and resistant, but no mass distinguishable Inguinal nodes about 3 by 4 cm in diameter

April 25, 1919 Abdominal masses faintly palpable Spleen felt 8 cm below costal margin, hard and firm No masses in neck

Third Admission—June 2, 1919 Since attack of influenza eight months ago, she has not been as well as before, and has lost 20 pounds in weight

Physical Examination—Deep and superficial lymph nodes above the left clavicle are enlarged The inguinal lymph nodes are enlarged, firm and smooth Spleen is palpable four finger-breadths below the costal margin

June 18, 1919, she was given by transfusion 450 cc blood, followed almost immediately by a severe chill (Chart 3)

During most of her stay in the hospital, the temperature was between 100 and 103 F, but finally it came down to normal She was given four roentgen-ray treatments which were followed with some reaction (Chart 3) Her general condition gradually improved, and she was discharged June 27, 1919

Interval History—July 16, 1919 Tenderness over spleen, signs of mediastinal mass

September 11 The patient returned to the dispensary complaining of abdominal pain, obstinate constipation, chills and fever She has had six roentgen-ray treatments since her discharge June 27, 1919 After each treatment she had general malaise, sick headaches, fever and nausea

Fourth Admission—Sept 11, 1919 She has had a gnawing pain in the back, not affected by respiration Temperature was elevated in the evening, low in the morning The pain in the splenic region was made worse by respiration Constipation increased this pain Constipation was very obstinate and not relieved by medication which made the pain worse The fever has lasted over periods of from three to five weeks, with afebrile intervals The febrile periods have been increasing in length Fever accompanied by drenching night sweats

Physical Examination—Glands One postcervical gland on the left side was firm and about the size of a peach stone A few small glands were palpable in the right axilla Abdomen Liver, 2.5 cm below costal margin Spleen, 8 cm below costal margin and 4 cm to left of midline Dulness extends up to fifth space Spleen was hard and quite tender, moved freely with respirations No other masses were felt in abdomen

Clinical Course—September 14, signs of fluid in the left pleural cavity were made out, and the next day 100 cc of yellowish turbid fluid was aspirated Signs of fluid again appeared and October 14, 900 cc of turbid fluid was removed from the left chest After the third transfusion (October 16) the patient's condition improved and the temperature came down to normal

November 6 Left pleural cavity was aspirated, and 700 cc fluid was withdrawn

November 30 The spleen was larger than previously, edge sharp, hard and irregular

December 9 Left eye Fluid vitreous was filled with opacities Retina detached at lower part Disk partly atrophic Right eye Patch of mild chorioretinitis found Floating opacities in vitreous

There were always signs of fluid in the left chest and at times also in the right chest. The patient complained frequently of pain in the right side of the chest and also in the splenic region. There was abdominal distention which was only slightly relieved by enemas, etc. The spleen was enlarged and tender. The temperature would be elevated for about two weeks, then descend gradually to normal and remain so for from ten days to four weeks, then rise again. During febrile periods, constipation was obstinate and there



Fig 2—Hodgkin's disease Involvement of peritoneum

was severe abdominal pain with distention. In the afebrile periods, she seemed to be much better. Because of weakness roentgen-ray treatments were discontinued after March 10, 1920.

After transfusions, of which she had nine, there occurred—with one exception—a sharp rise in temperature. Immediately after this rise the temperature went down rapidly to a lower level than it reached prior to transfusion. This drop in temperature was accompanied by improvement in general symptoms.

August 27 an operation for intestinal obstruction was considered but was not done because the patient was relieved by turpentine enemas given in the knee chest position.

September 25, she complained of gas in the intestines with cramps. The abdomen showed only moderate distention and was soft and tender. Treatment was unavailing. She gradually grew weaker and died without reacting to stimulants.

Final Diagnosis—Hodgkin's disease

Necropsy Report (9061) —Anatomic diagnosis. Hodgkin's disease, with involvement of the spleen, liver, lungs, pleura, intestine and peritoneum, ulceration of colon, perforation of transverse colon, acute generalized peritonitis, left hydrothorax, fibrous pleural adhesions, chronic mitral endocarditis.

The body is that of a well developed, moderately emaciated white woman, 152 cm in length. The mucous membranes are pale. Superficial lymph glands are not palpable. The abdomen is distended and tense. There is an old scar in the midline between the umbilicus and pubis. There is some edema of the feet.

ABDOMINAL CAVITY—The abdominal cavity contained a considerable quantity of foul gas and 500 cc of thick dark greenish fluid, having a foul, fecal odor. The omentum is adherent along the scar in the anterior abdominal wall and also to the parietal peritoneum in the left lower quadrant. The peritoneum is thickened and opaque, especially that part in the pelvis and both lower abdominal quadrants. At the splenic flexure is a firm mass measuring 12 by 8 cm. It is adherent to the parietal peritoneum, and behind it the colon seems to pass.

Intestine. Adjacent loops of intestine are lightly bound together by a fibrino-purulent exudate. Over the serous surface of the sigmoid and its mesentery and also the pelvic peritoneum are numerous nodules, varying in size from a few millimeters to 1 centimeter or more in diameter. These nodules are firm and often fused together. The nodules are most abundant along the mesenteric attachment of the sigmoid, and spread down over its serous surface, often as stiff plaques 2 cm in length, and at a few places they almost encircle the intestine (Fig 2). On section, they are silver gray in color and translucent.

The mucosa of the small intestine is negative. The lymphoid follicles and Peyer's patches are made out with difficulty. The ascending colon and the proximal half of the transverse colon are normal. In the distal half of the transverse colon are many ulcers in the mucosa, varying from 0.5 to 1.5 cm or more in diameter. These are rounded or oval, with shelving edges and clean bases, and rarely extend deeper than the muscularis. One of the large ulcers on the inferior wall has perforated, the opening being more than 1 cm in diameter. At the splenic flexure, the intestine is very sharply angulated and the lumen is much narrowed. The wall of the intestine in this region is tremendously thickened, very stiff and almost cartilaginous in consistence. In the wall of the intestine, usually in the serous portion, are many firm nodules about 0.5 cm in diameter. The fat about the intestine contains similar nodules, and fibrous tissue is increased in it. (It was this infiltrated fat and thickened intestinal wall which was described as the mass at the splenic flexure, and also clinically as the spleen.) The mucosa of the descending colon and sigmoid contains many ulcers, similar to those described above. The rectum is negative except for a few nodules in the peritoneum over it.

STOMACH AND DUODENUM. Stomach is negative, except for a stellate scar in the mucosa on the lesser curvature, and a few nodules similar to those described above in the serosa, also along the lesser curvature. The duodenum shows nothing unusual.

LYMPH GLANDS. The mesenteric lymph glands are quite small and are found with difficulty. On section, nothing abnormal can be made out. The retroperitoneal glands are not enlarged, they are quite fibrous. The pelvic lymph glands are bound together by fibrous tissue. Some of them are fibrous, others contain firm, yellow opaque material. They are not enlarged. Along the thoracic aorta are a few firm glands which on section contain considerable fibrous tissue. The mediastinal glands are only slightly enlarged. Those at the bifurcation of the trachea show an increase in fibrous tissue. Below the manubrium is a lymph gland which is slightly enlarged and soft. On section

it is gray and translucent, with black pigment scattered through it. The cervical and axillary glands are quite small and on section show nothing unusual.

SPLEEN—The spleen does not extend below the costal margin. It weighs 200 gm., has a definitely nodular feel. On section there are seen in the pale grayish red pulp many moderately firm, opaque, white, sharply circumscribed masses, measuring up to 1 cm. in diameter, and having a somewhat lobulated outline. The malpighian bodies are not easily seen. There is no apparent increase in fibrous tissue.

LIVER The liver weighs 1,450 gm., and measures 22 by 21 by 9 cm. The capsule is smooth. Projecting above the surface are several white rounded

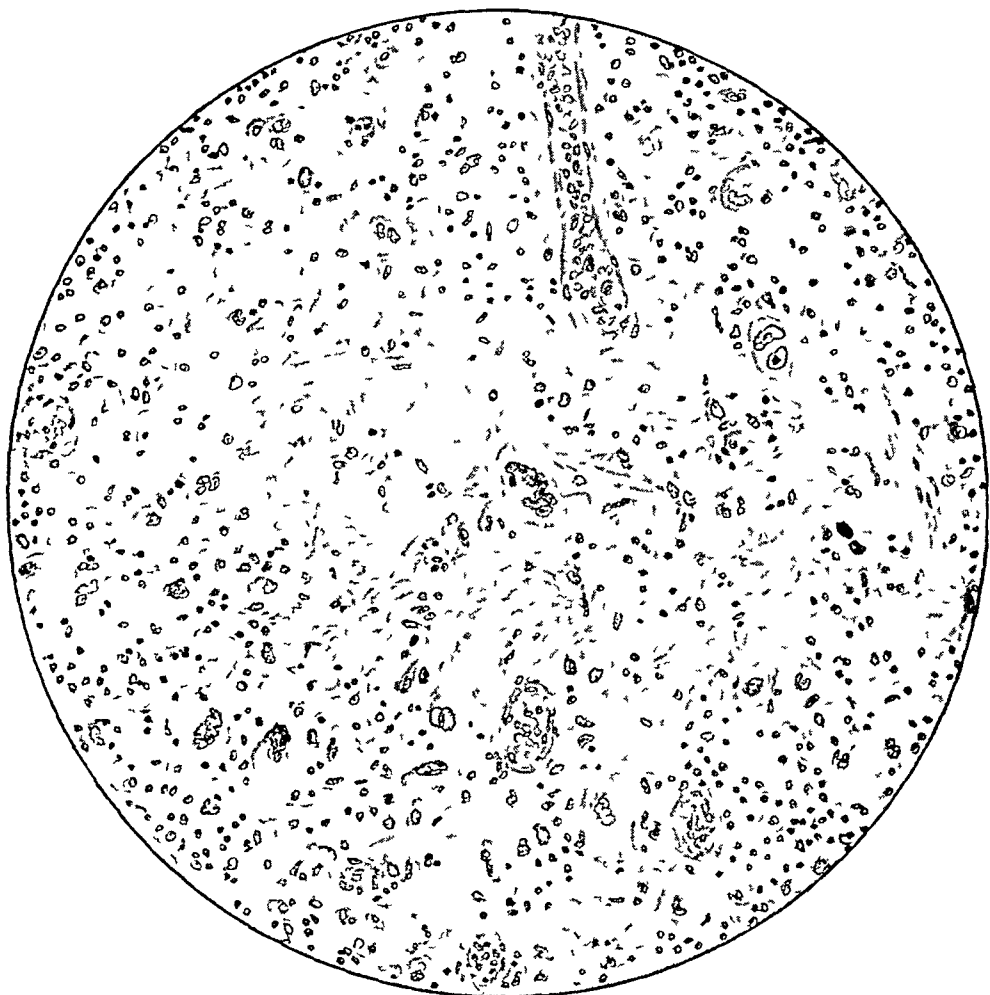


Fig. 3—Hodgkin's disease. Gland from axilla.

nodules, the largest of which is in the postero-inferior part of the right lobe. On section, the pale reddish yellow surface is thickly studded with nodules varying in size from 1 mm. to one 3 cm. in its greatest diameter. The smaller nodules are gray and translucent, the larger ones are opaque and white. For the most part they are rounded, soft and sharply circumscribed. The large mass in the right lobe is soft, opaque and yellowish white, with a somewhat irregular outline. There is another large, similar mass close to the falciform ligament. The lobulation of the liver is uniform. There is no increase in connective tissue. The gallbladder is negative.

PANCREAS The pancreas weighs 100 gm. The tail is densely adherent to the firm mass at the splenic flexure. This portion contains much fibrous tissue running in wide strands through the parenchyma. Elsewhere, the pancreas is normal.

UTERUS Normal.

OVARIES The ovaries are quite small and fibrous, resembling in appearance the ovaries of an elderly woman. On section, a few corpora albicantia are seen. No follicles or corpora lutea are made out.

BLADDER Negative, except for nodules in the peritoneum over it.

Aorta, kidneys, suprarenals and fallopian tubes are normal.

HEART Weight, 210 gm. It is normal, except for a few firm fibrous nodules on the mitral valve.

LUNGS The left pleural cavity contains 400 c.c. of straw colored fluid. The right pleural cavity contains only a slight excess. Left lung. There are some dense adhesions between the apex of the lower lobe and the parietal pleura. The lung is crepitant, except for a firm area in the anterior part of the lower lobe. On section through this area, there is seen a small, firm, gray nodule surrounded by a zone of consolidation. Elsewhere the lung shows nothing unusual on section. In the parietal pleura at the site of the adhesions, there are many firm elevated nodules, resembling those seen in the peritoneum. These are grouped together and cover an area measuring about 6 by 4 cm. Right lung. Normal. The bronchial lymph glands are not enlarged and are quite black in color.

THYROID Is slightly enlarged and firm. On section considerable colloid is seen.

Bacteriologic Report—On culture, the peritoneal fluid contained *B. welchii*, enterococci, small gram-positive bacilli, *B. coli communis*, and *B. fecalis alkaligenes*.

Microscopic Examination—**LYMPH GLANDS** Axillary and cervical. The normal arrangement of the gland is lost, the germinal centers and sinuses are obliterated, the lymphocytes are reduced in number. Scattered throughout are many large cells, with one or more oval or indented vesicular nuclei, each containing a small amount of chromatin material and a single large nucleolus. Also, there are many multinucleated giant cells, having oval, rounded or lobed nuclei which appear to be solid. There is little increase in connective tissue. A few small necrotic areas are seen containing fibrin. The capsule is slightly thickened. There are no eosinophils. In the fat about the gland are small accumulations of plasma cells and lymphocytes (Fig. 3).

Retromammary The lymphoid tissue has been almost entirely replaced by loose connective tissue, masses of giant cells with hyperchromatic nuclei, and endothelioid cells. In this new tissue are many small foci of necrosis, infiltrated with polymorphonuclear neutrophils. At one point, the capsule of the gland has been penetrated and the giant cells and connective tissue have extended into the surrounding fat. No eosinophils are seen.

Mesenteric The germinal centers and sinuses are obliterated. The lymphoid tissue is rather loose. The capillaries in the gland are distended. There are many typical endothelioid cells. In some of these the nucleus has a vacuolated appearance, the nucleolus having disappeared. Only a few cells are present which have the hyperchromatic nuclei. A few areas of necrosis are found in which the cell outlines can still be discerned. The capsule has been invaded and in the surrounding fat are found giant cells, lymphoid and plasma cells and endothelioid cells. Occasionally, a single endothelioid cell is found lying free inside a fat cell.

Retroperitoneal In one section, fibrous tissue is tremendously increased and passes in dense and wide bands throughout the gland, and also is scattered diffusely through it. Between the larger bands of fibrous tissue are small pockets of lymphoid cells, among which are found typical endothelioid cells.

and a few of the giant cells with densely staining nuclei. In another section, the fibrosis is even more marked; there are fewer endothelioid cells. A moderate number of polymorphonuclear neutrophils are found.

Pelvic. The greater portion of the gland consists of caseous material, in which are found nuclear fragments and cholesterol crystal clefts. About the periphery of this necrotic area are a few epithelioid cells and mononuclear phagocytes containing brown pigment. There are also irregular masses staining blue, lying in clear spaces having the outlines of cells. With silver nitrate and purpurin preparations these are found to be masses of calcium, and are most probably calcified nuclei.

In sections of glands stained with the Wilson stain the nucleoli of the typical endothelioid cells stain with varying intensity with eosin. Often in the other giant cells a large nucleolus stands out brilliantly stained with eosin in the center of the solid blue staining nucleus. The cytoplasm of these latter cells likewise takes a more intense stain with eosin than does that of the endothelioid cells (Fig 4).

SPLFEN. The sinuses are rather wide and connective tissue is increased. Accumulations of endothelioid cells and polymorphonuclear leukocytes, together

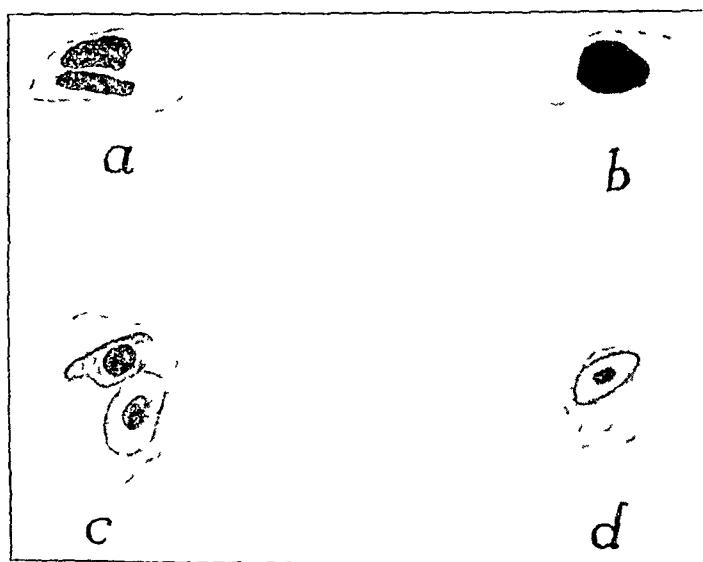


Fig 4—Hodgkin's disease. a and b, atypical giant cells, hematoxylin and eosin stain. c, atypical giant cell, Wilson stain. d, endothelioid cell.

with eosinophils often occupy the site of the malpighian bodies. In some of these there is necrosis of the central part. Several of the vessels are surrounded by masses of the Hodgkin's granulation tissue.

PANCREAS. The interlobular septa are widened by an increase in dense connective tissue in which are accumulations of small wandering cells and occasionally a few of the giant cells with hyperchromatic nuclei and typical endothelioid cells. The parenchyma and islands are normal.

LIVER. In many of the lobules the cells about the portal areas are filled with fat. There are masses of loose connective tissue in which are many large cells with multiple hyperchromatic nuclei. A few eosinophils are found in these groups. In the larger of these there is often central necrosis. At the margins of some of the nodules, the giant cells are found out in the sinusoids, and the liver cells about them are indented or flattened out. Occasionally giant cells are also found in sinusoids at a distance from the nodules.

KIDNEY. Normal.

SUPRARENAL. Normal.

SMALL INTESTINE Normal, except for a fibrinopurulent exudate on the serous surface

COLON In the lymphoid follicles are seen many of the giant cells with densely staining nuclei. In the submucosa are large masses of loose connective tissue and small round cells, with intermingled giant cells. In some of the larger masses, the central portion has undergone necrosis. In the serosa and surrounding fat are seen large accumulations of the giant cells with hyperchromatic nuclei, and virtually none of the characteristic endothelioid cells. The giant cells are found extending up between the muscle bundles of the longitudinal muscle although generally the muscle is lifted up by the new growth of tissue. The new tissue also extends to the blood vessels, but does not invade the vessel wall. A few eosinophils are found.

OVARY The blood vessels stand out prominently. Several corpora albicantia are present which have a much less compact appearance than usual. Also there are several areas which appear to be recent corpora albicantia, but which contain great numbers of cells loaded with coarse brown granules. No follicles are to be differentiated.

HEART The myocardium is normal.

LUNG Just beneath the pleura are several groups of alveoli having thickened walls. Some of the alveolar spaces are filled with a granular material and a few small mononuclear cells. Others are full of small wandering cells and among these are typical endothelioid cells and a few of the giant cells with dense nuclei.

PARIETAL PLEURA This is greatly thickened and edematous. There is a diffuse infiltration with small round cells, polymorphonuclear neutrophils, and large mononuclear cells. Dense accumulations of small round cells, many having hyperchromatic nuclei, are scattered through the section, but especially just beneath the pleural surface.

Treatment—Aside from sedatives, the only therapeutic measures used were transfusions and the roentgen-ray.

TRANSFUSIONS Nine transfusions were given. At first they were given because of the severe anemia and weakness. Immediately after transfusion there was a rise of temperature and a chill six out of nine times. In a few hours, however, the temperature would fall and the patient would be much improved for from a few days to a month. It is impossible to say how much of this improvement was due to the treatment but undoubtedly the transfusions had a definite, if limited, beneficial effect.

Some of the drops in the temperature were very striking, and the improvement in the general condition of the patient was just as marked. On only two occasions did the temperature remain elevated after transfusion. One of these occasions occurred just before death.

ROENTGENOTHERAPY The patient was treated ninety-five times but in many cases more than one area was irradiated. This treatment was begun under the guidance of Dr. Corscaden. The Coolidge tube and Solace apparatus were used. The filters were changed several times. They were first, 3 mm aluminum, 1 cm wood, second, 1 mm aluminum, 1 cm wood, 3 mm glass, 4 mm leather, third, 1 mm aluminum, 1 cm wood, 3 mm glass, 4 mm leather, 2 mm bakelite, fourth, 1 mm aluminum, 1 cm wood, not used, 4 mm leather, 2 mm bakelite. The voltage was 80 or 90 kilovolts. The current was 5 milliamperes. Anodal distance from skin, 25 cm. Dosage at first was 45 milliamperes minutes, this was increased to 50, and at the last reduced to 35 milliamperes.

The whole of the body, anterior and posterior, was divided into areas. The numbers of these areas were changed from time to time but were always so arranged that all the contents of the thorax and abdominal cavity were exposed to the rays.

Originally the plan was to have the patient treated twice a week, choosing the areas so that the whole of the trunk would be irradiated once in three

weeks. Owing to the fact that the patient was not always in the hospital, it was frequently found impossible to adhere to this plan.

Frequently the treatments were followed by nausea and vomiting, this reaction would last for a few hours.

Because of the low white blood cell count (between 3,000 and 4,000) and general weakness, the patient was given no roentgenotherapy for six months prior to death.

DISCUSSION

Roentgenotherapy was first used in the treatment of Hodgkin's disease about 1900. Among the first to report cases were Pusey,⁶ and Williams⁷ in 1902. The following year Childs,⁸ and Finch⁹ contributed to the literature. Three years later Pfeiffer¹⁰ wrote an article. These early papers are interesting but frequently lacking in details. Indeed, in some instances they are only brief letters expressing the writer's views in regard to his results.

Among the more recent writers are Hocguertel,¹¹ Krecke,¹² Sanguinetti,¹³ Holding,¹⁴ Levin¹⁵ and Knox¹⁶. It is unfortunate that none of these observers report the effect of the roentgen ray on the glands. In a paper just published Mueller¹⁷ describes two cases, detailing the microscopic appearance of the glands after treatment.

Our patient was treated ninety-five times with roentgen rays. It is impossible to say just what effect this had on the course of the disease, apparently, the glands decreased in size, especially the cervical nodes. As is frequently the case, the patient was usually nauseated and occasionally vomited after the treatment. This discomfort generally lasted for several hours. After the immediate effect of the treatment wore off, the patient would often seem to feel better and it was believed that the rays had a beneficial effect.

Course—The progress of the disease may be described as being slowly progressive, there were periods when she would be very ill. These periods would be followed by intervals when she would feel much better. As time went on, the acute stages became longer and the improvement less marked. The loss of weight was constant. The transfusions evidently helped her, but the effect was not lasting.

6 Pusey, W. A. J. A. M. A. **38** 166 (July 18) 1902.

7 Williams, F. H. Boston M. & S. J. **147** 365, 1902.

8 Childs, B. C. Med. News **4** 143, 1903.

9 Finch, C. B. J. Cutan. Dis. including Syph. **21** 562, 1903. Finch, C. B. Med. Rec. **65**.773 (May 14) 1904.

10 Pfeiffer, C. P. Beitr. z. klin. Chir. **50** 262, 1906.

11 Hocguertel, J. M. Fortsch. a. d. g. der Roentgenstrahlen **21** 638, 1913.

12 Krecke, A. Beitr. z. klin. Chir. **95** 609, 1914.

13 Sanguinetti, H. H. Univ. Med. Rec., Lond. **6** 299, 1914.

14 Holding, H. F. Ann. Surg. **65** 686, 1917.

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17 Mueller, T. J. M. Research **42** 325, 1921.

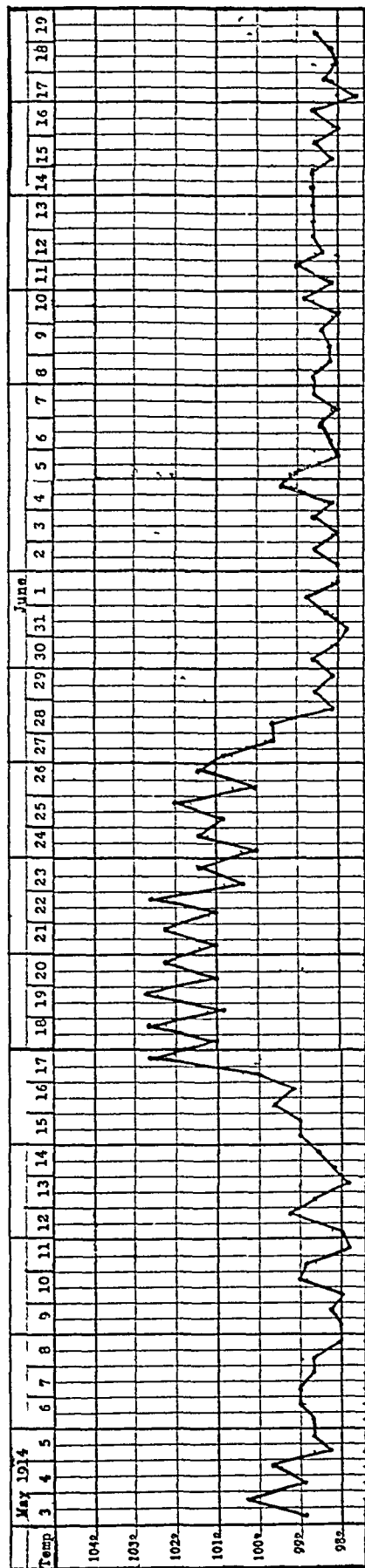
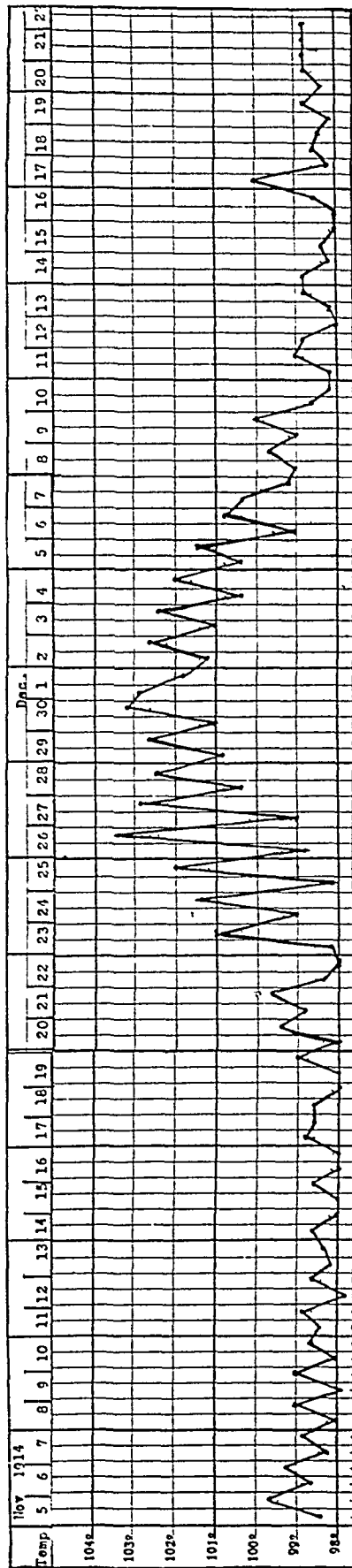


Chart 1

The temperature charts are given at such length, because it is very interesting to see the constant remissions, as well as falls in temperature occasioned by transfusions. Charts 1 and 2 were made at the time of the first admission and antedated the others by more than five years. Beginning with Chart 3, the whole of the record of the last admission is shown. Radiotherapy Trans = transfusion Aspir = aspiration



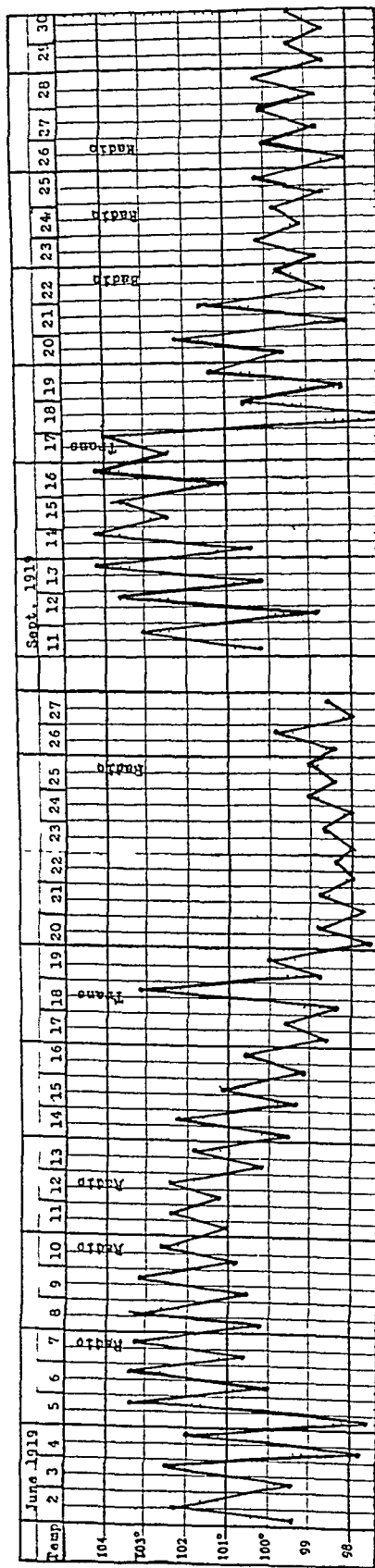


Chart 3

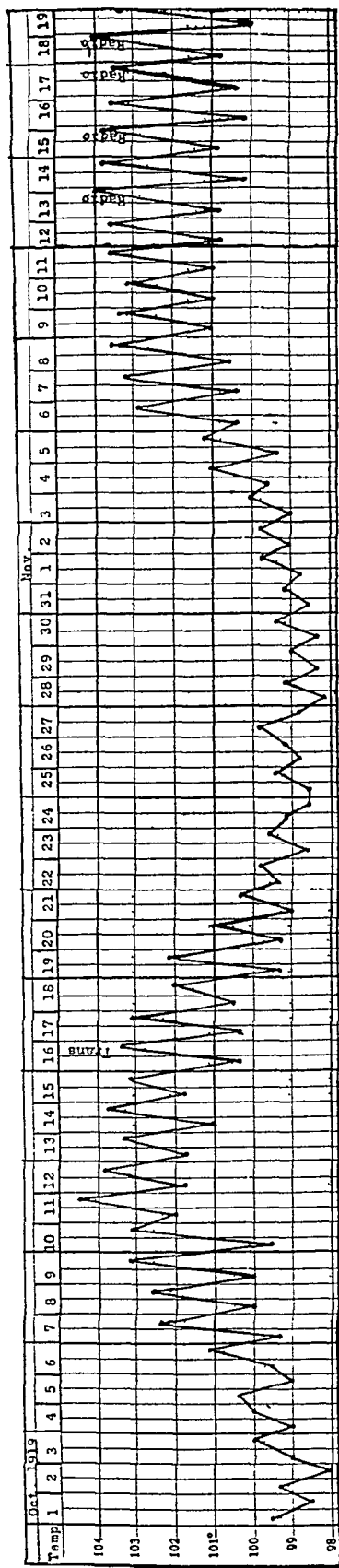


Chart 4

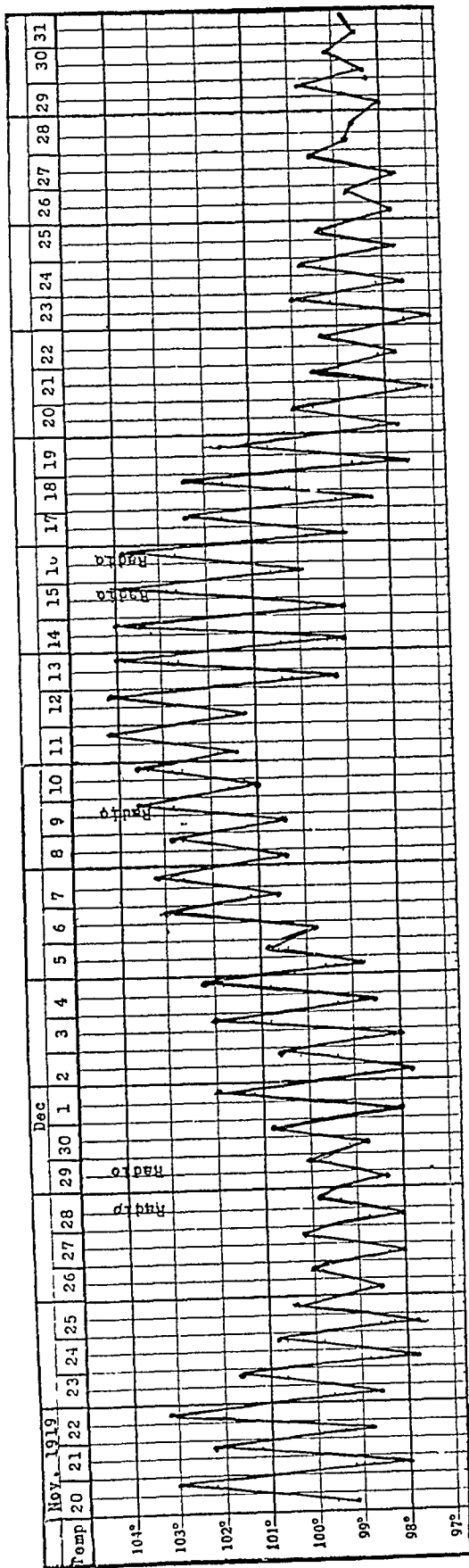


Chart 5

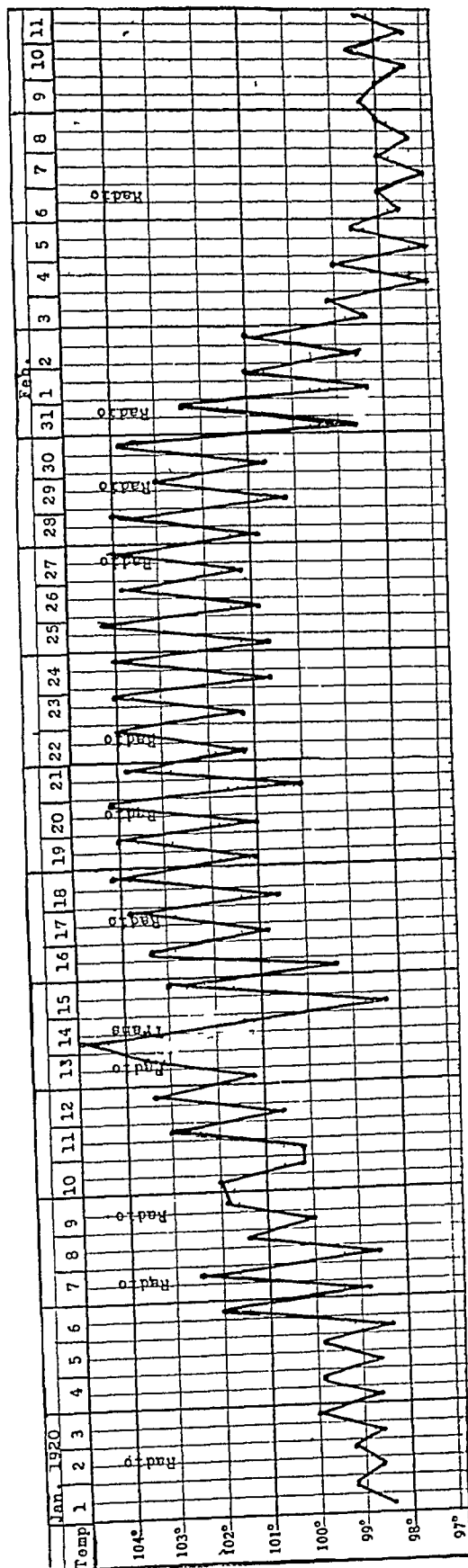


Chart 6

Fever—When first seen, she ran an intermittent temperature similar to that described by Ebstein,¹⁸ Murchison,¹⁹ Pel,²⁰ Ziegler²¹ and Musser² (Charts 1 and 2) Then for varying intervals, there would be no fever, and after a while the recurrent type would reappear During the last admission the recurrent type was the rule (Charts 3 to 11) The temperature was, apparently, affected by the roentgen ray and the transfusions, but it is doubtful if either of these measures had any real effect on the course of the fever Although she had been having a high fever for almost a month just before she died, on other occasions she had just as high a temperature and it lasted for a similar period (Chart 6)

Blood Counts—The blood examination is interesting because the picture resembled that described by Bunting²² in Hodgkin's disease There usually was an increase in the white blood cells during the first admission, the total count was as high as 12,000 The large mononuclear

TABLE 1—EFFECTS OF TRANSFUSIONS

Transfusion	C c	Red Blood Cells		Hemoglobin, per Cent	
		Before	After	Before	After
First	450	3,800,000	4,500,000	65	70
Second	400	3,100,000	3,700,000	50	65
Third	350	2,700,000	3,600,000	50	55
Fourth	300	2,600,000	3,200,000	40	40
Fifth	300	3,600,000	4,600,000	40	60
Sixth	300	3,500,000	3,100,000	60	60*
Seventh	300	1,800,000	2,200,000	40	50
Eighth	300	4,500,000	Not done	75	
Ninth	250	1,700,000		35†	

* Not taken immediately after transfusion

† The patient died the next day

cells and transitionals were increased The platelets were always increased, running as high as 570,000, even after many treatments with the roentgen rays

Later the white cells were reduced as low as 2,200 This was thought to be due to the effect of the irradiation and on this account the treatment was stopped

The anemia was progressive and very marked toward the end of the illness During the first year, the red cells numbered as high as 4,800,000, with 81 per cent hemoglobin The anemia increased until a few days before death, when the red cells numbered 1,700,000, and the hemoglobin was 35 per cent

The effects of the transfusions are shown in Table 1

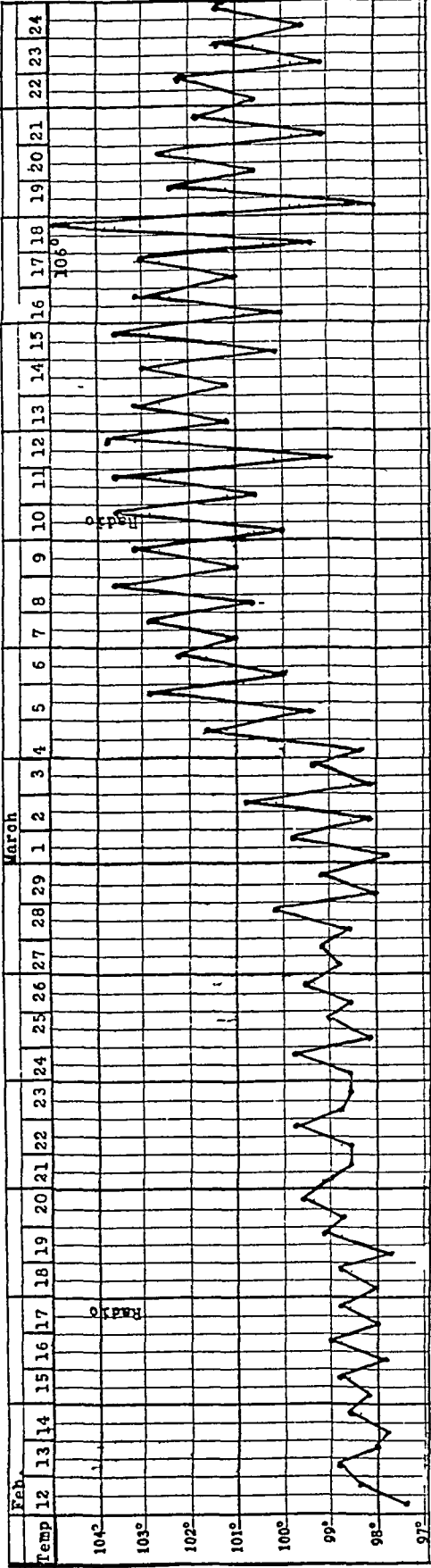
18 Ebstein, W Berl klin Wchnschr **24** 565, 1887

19 Murchison, C Tr Path Soc Lond **24** 372, 1870

20 Pel P K Berl klin Wchnschr **24** 644, 1887

21 Ziegler Die Hodgkinsche Krankheit, Jena, G Fisher 1911

22 Bunting, C H Tr Assn Am Phys **26** 435, 1911, Bull Johns Hopkins Hosp **25** 173 1914



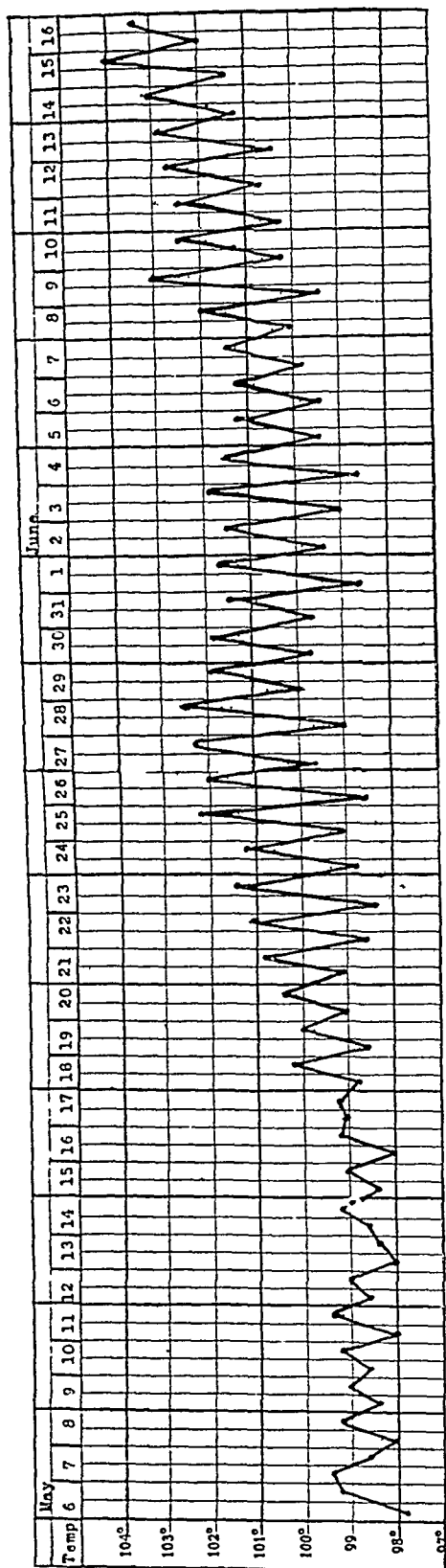


Chart 9

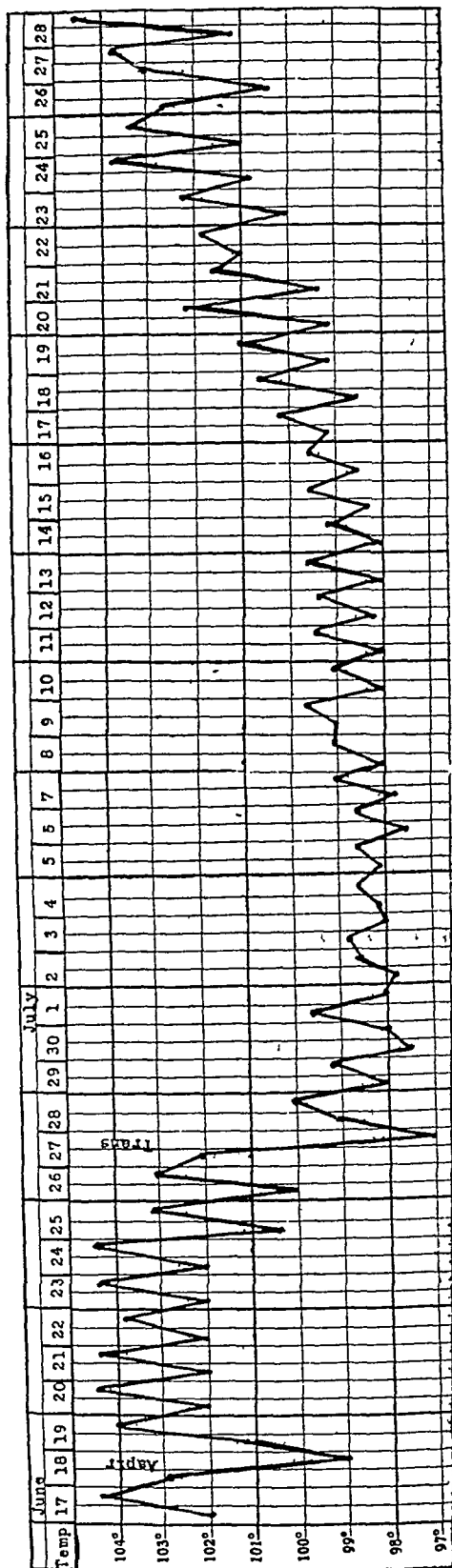


Chart 10

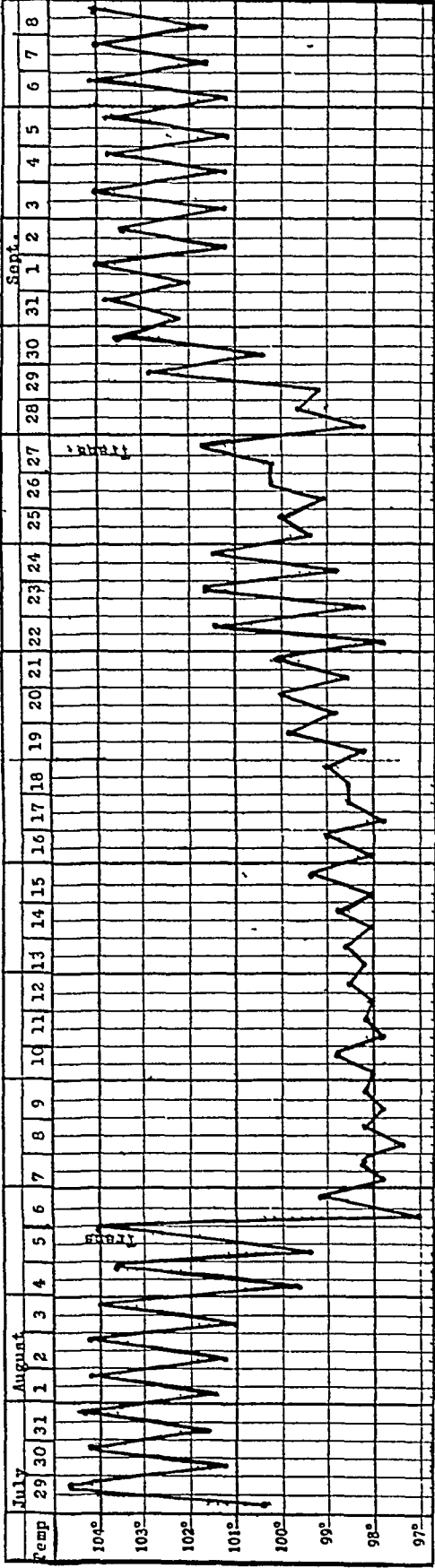


Chart 11

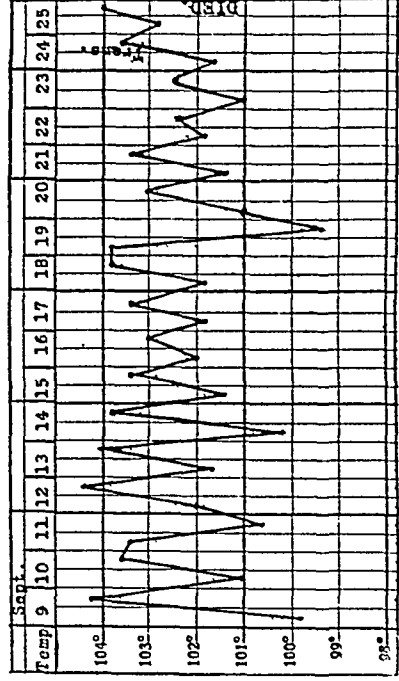


Chart 12

It is unfortunate that the data are not more complete. However, they show that the transfusions had a beneficial, if temporary, effect on the red cells and the hemoglobin. It is very difficult to account for the change between the seventh and eighth transfusions. The increase of more than 2,000,000 cells, and of 25 per cent in the hemoglobin

TABLE 2—BLOOD COUNTS

Date	Transfusion, Cc	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorpho- nuclears, per Cent	Basophils, per Cent	Eosinophils, per Cent	Small Lym- phocytes, per Cent	Large Lym- phocytes, per Cent	Large Mono- nuclears per Cent	Transfusions, per Cent	Platelets
1914												
3/ 7		4 090 000	60	10 000	75		1	24				
7/ 7		4 000 000	74	12,800	74							
11/28		4,880,000	81	10 000	75			25				
1915												
3/ 1		4,540,000		8 140	71	0.5	5.5	14			9	
11/14		4,430 000	85	9 500	75.5	1.5	0.5	14.5		4.5		
1919												
1/15		4 470,000	50	5 000	72			2.0	23	3		
6/ 4		3,800,000	65	3 800	72		1	3.0		21	3	
6/18	450											
6/20		4,450 000	70	4 300	74		2.0	13.0	10	1		496,000
6/24		4,400 000	80	4 200	74		2.0	8.0		9	7	
7/23		3,900,000	73	5 700								
9/10				6,800	67			10	20		3	
9/16		3,100,000	50	5 600								
9/17	400											
9/19		3,700 000	65	9,200	80.5		0.5	18.5		0.5		
9/22		3 300 000	60	5,200	77		0.5	20.5		0.5	1.5	
9/30		4 300,000	65	6,800	83						2	
10/15		2,700,000	50	6 400	85			10	4		1	
10/16	350											
10/20		3 640 000	55									
11/12		3,870 000	60									
12/11		3,810 000	60-70	10 000	79.6	0.2	0.2	3.0		34	13.6	340,000
1920												
1/12		2 600,000	40	4 700								
1/14	300											
1/17		3 240 000	40									
2/ 4		3 200,000										
2/11				3,700	77	0.4	1.2	8.8		2.4	9.4	520,000
3/13		3 200 000	50									
3/16				2,200								
4/ 2		3,600 000	40									
4/ 2	300											
4/ 8		4 640,000	60	3 600	55		1	44		1		
5/11		3,500 000	60-70	6,000	55	1	1	43				
5/12				9,200	78.4	0.8	3	13		0	4.8	570,000
6/18				6 000	71.2	0	0.2	14.2		1.2	5.6	520,000*
6/27	300											
7/22		3 100 000	60	5,700	71			8	21			
8/ 5		1,800,000	40	6 050								
8/ 5	300											
8/ 6		2,300 000	50	3,200								
8/10		3 030,000	60	4 200								
8/27		4,500,000	75	7,900	72			28				
8/27	300											
9/23		1,750 000	35	5,600								
9/24	250											

* Unclassified 76

seems rather improbable, especially as the patient did not seem to be any better. It is impossible to exclude the possibility of a technical error.

Symptoms and Physical Signs—The blood pressure was always low, even in the early part of the disease when the patient was up

and about This has been observed in Hodgkin's disease before (Longcope and McAlpin²³), and is of interest but probably not of any great importance

Hydrothorax It was necessary to aspirate the chest four times during the last admission This condition is frequently found in Hodgkin's disease, and has been mentioned by Ziegler,²¹ Edsall,²⁴ Lemon and Doyle,²⁵ and by Longcope and McAlpin²⁶ It is probably due to involvement of the pleura The chest was aspirated three weeks before death, and at the postmortem examination the left pleural cavity contained 400 c c of straw colored fluid

Abdominal Symptoms—For several months before death, the patient complained of pain in her right side, and in this region a large mass was readily palpated It was supposed to be the spleen, and the pain was attributed to a perisplenitis The necropsy showed the spleen to be only slightly enlarged (weight 200 gm), but there was a large mass made up of infiltrated fat and intestinal wall that had been mistaken for the spleen

About fifteen months before death, the patient began to complain of abdominal pain During these attacks the abdomen would become distended Relief was obtained by various therapeutic measures, such as lavage, cathartics (in the early stages) and edemas At first these attacks were of short duration and not very serious, but during the last few weeks they became a great problem Finally, it was deemed advisable to operate, although the patient was an extremely poor surgical risk Before this was done, an enema was given in the "knee chest" position, with satisfactory result The relief was only temporary and in a few days the symptoms returned The patient was in great distress, requiring sedatives She became very weak, did not react to stimulants and died

RÉSUMÉ

1 The diagnosis of Hodgkin's disease of the mesenteric lymph nodes was made six and one half years before death The patient was under observation from the time the diagnosis was made until she died

2 The temperature at times was of the recurrent type, described by Ebstein,¹⁸ Murchison,¹⁹ Pel²⁰ and Ziegler²¹

3 The blood picture closely resembled that described by Bunting²²

4 The blood pressure was very low, even when the patient was first admitted (Longcope and McAlpin²³)

23 Longcope, W T, and McAlpin, K R Oxford Med 4 20

24 Edsall, D L New York M J 82 838, 1905

25 Lemon, W S, and Doyle Am J M Sc 172 516, 1921

26 Longcope, W T, and McAlpin, K R Oxford Med 4 17

5 Although the spleen was thought to be very much enlarged during life, at necropsy it was found to be only a trifle larger than normal. Apparently a mass of infiltrated fat and intestinal wall had been mistaken for the spleen.

6 The hydrothorax that required paracentesis is not unusual in this disease, and is probably due to involvement of the pleura. Cases have been described by Lemon and Doyle,²⁵ Ziegler,²¹ Longcope and McAlpin.²⁶

7 Because of the advanced stage of the disease when the diagnosis was made, it is safe to say that the roentgenotherapy slowed the process but in no sense cured the condition.

8 Death was due to perforation of the intestine. This is believed to be very unusual in Hodgkin's disease.

9 Unusual pathologic findings are: Extensive involvement of the peritoneum and abdominal viscera, the tendency to regional invasiveness, atypical giant cells and the scarcity of eosinophils.

We are deeply indebted to Dr. Warfield T. Longcope and Dr. A. M. Pappenheimer for suggestions and advice.

EXPERIMENTAL REPRODUCTION OF THE SPECIFIC HISTOPATHOLOGY OF INFLUENZA *

GEORGE BAEHR, M.D., AND LEO LOEWE, M.D.

NEW YORK

It was realized rather early in the recent pandemic of influenza that by the time patients died secondary infections with various pyogenic organisms had usually taken place, which more or less completely obliterated evidences of the original disease. From numerous bacteriologic studies, it was evident that the bacteria recovered from the lungs after death had secondarily invaded the damaged organs from the upper respiratory tract. Traditional belief made many observers reluctant to assign a similar rôle to the *B. influenzae* of Pfeiffer. But even this organism was finally relegated to a secondary rôle by work such as that of MacCallum,¹ which demonstrated that although it might be present in a large percentage of the lungs of persons dying of the disease in one part of the country, the bacillus of Pfeiffer was correspondingly rare in the lungs in other parts of the country where, at the time, it happened to be a less frequent resident of the upper respiratory tract.

Such advances in our knowledge of the bacteriology of the disease immediately concentrated the efforts of pathologists on an attempt to differentiate the secondary purulent from the primary fundamental lesions of epidemic influenza. The best work in this country (Klotz,² Winternitz, Wason and MacNamara³) kept this aim constantly in view, as did the best of the European observers (Oberndorfer,⁴ Dietrich,⁵ Glaus and Fritzsche,⁶ Marchand,⁷ Soerensen,⁸ Koopman⁹). Some of these authors (Klotz, Oberndorfer, Glaus and Fritzsche, Koopman) had the unusual opportunity to study fulminating cases of the disease in persons who had died within forty-eight hours after the onset, before the secondary infection had sufficiently invaded the damaged lung to obscure the primary pathological picture.

* From the Pathological Department of the Mount Sinai Hospital.

* Work done during the tenure of a George Blumenthal, Jr. fellowship in pathology.

1 MacCallum. J. A. M. A. **72** 720 (March 8) 1919.

2 Klotz. Studies on Epidemic Influenza, Published from University of Pittsburgh School of Medicine, 1919, p. 207.

3 Winternitz, Wason and MacNamara. The Pathology of Influenza, Yale University Press, 1920.

4 Oberndorfer. Munchen med. Wchnschr. **65** 30, 1918.

5 Dietrich. Munchen med. Wchnschr. **65** 34, 1918.

6 Glaus and Fritzsche. Cor.-Bl. f. Schweiz. Aerzte **48** 1121, 1918, *ibid* **49** 72 1919.

7 Marchand. Munchen med. Wchnschr. **66** 5, 1919.

8 Soerensen. Ztschr. f. Hygiene u. Infectiönskr. **91** 204, 1921.

9 Koopman. Virchows Arch. f. path. Anat. **228** 319 1920.

Specificity of the Histopathology of Early Human Influenza — Summarizing the work of these authors, one is impressed with the unanimity of their opinion that the pathologic process in early human influenza represents a specific tissue reaction, not to be seen in the lungs in any other type of infection. In fact, Winternitz and his collaborators state in their monograph "The histology of this disease is almost as specific as that of any biologic reaction"

The essential features of the pathologic lesions in early human influenza are (1) congestion, edema and often minute hemorrhages in the mucous membrane of the trachea and larger bronchi, (2) patchy distribution of the pulmonary lesions, (3) diffuseness of the process, which often extends through several lobes or even parts of all lobes; (4) profuse serosanguinous exudate which drips from the moist cut surface of involved parenchyma, (5) hemorrhagic character of the lesion, the hemorrhagic exudate being seen microscopically to infiltrate the interstitial tissue and fill patches of alveoli, (6) aplastic character of the process, the inflammatory exudate in alveoli and interalveolar interstitial tissue being composed almost entirely of red cells and serum with an occasional endothelial cell but containing astonishingly few polymorphonuclear or other leukocytes. In addition, Klotz directed special attention to the tendency to emphysematous overdistension of alveolar air spaces in the involved lungs, and Winternitz also emphasized the tendency to necrosis of the epithelium lining the trachea and bronchi and to hyalin necrosis of pulmonary tissue, especially of interalveolar septa in the damaged areas. One of us had considerable experience with the study of this unusual type of pulmonary inflammatory process, while serving during the pandemic as director of laboratories for the group of U S Army Base Hospitals at Beau Désert Hospital Center, France.

Experimental Reproduction of Influenza — Just as advances in bacteriology during the first year of the pandemic (1918) were in large part responsible for a more accurate conception of the pathologic phenomena involved in influenza, so, in similar manner, the more recent bacteriologic investigations of Olitsky and Gates¹⁰ and of Loewe and Zeman¹¹ have afforded renewed opportunities for a study of the essential features of this pathologic process. Independently of one another and simultaneously, these two groups of investigators succeeded in cultivating a filtrable virus from the nasopharyngeal washings made early in the course of the influenza, which is capable of producing lesions in the lungs of rabbits, grossly and microscopically identical with those found in human beings suffering from the disease.

10 Olitsky and Gates J. Exper. M. **33** 125, 1921

11 Loewe and Zeman J. A. M. A., **76** 986 (April 9) 1921

We have, therefore, undertaken to study more minutely the pathologic process induced experimental in these animals by the intratracheal inoculation of cultures of these punctiform, filtrable bodies and of influenza virus (filtered human nasopharyngeal washings or lungs from inoculated animals) In this manner we have been able to observe the lesions at the very earliest stages of their development, an

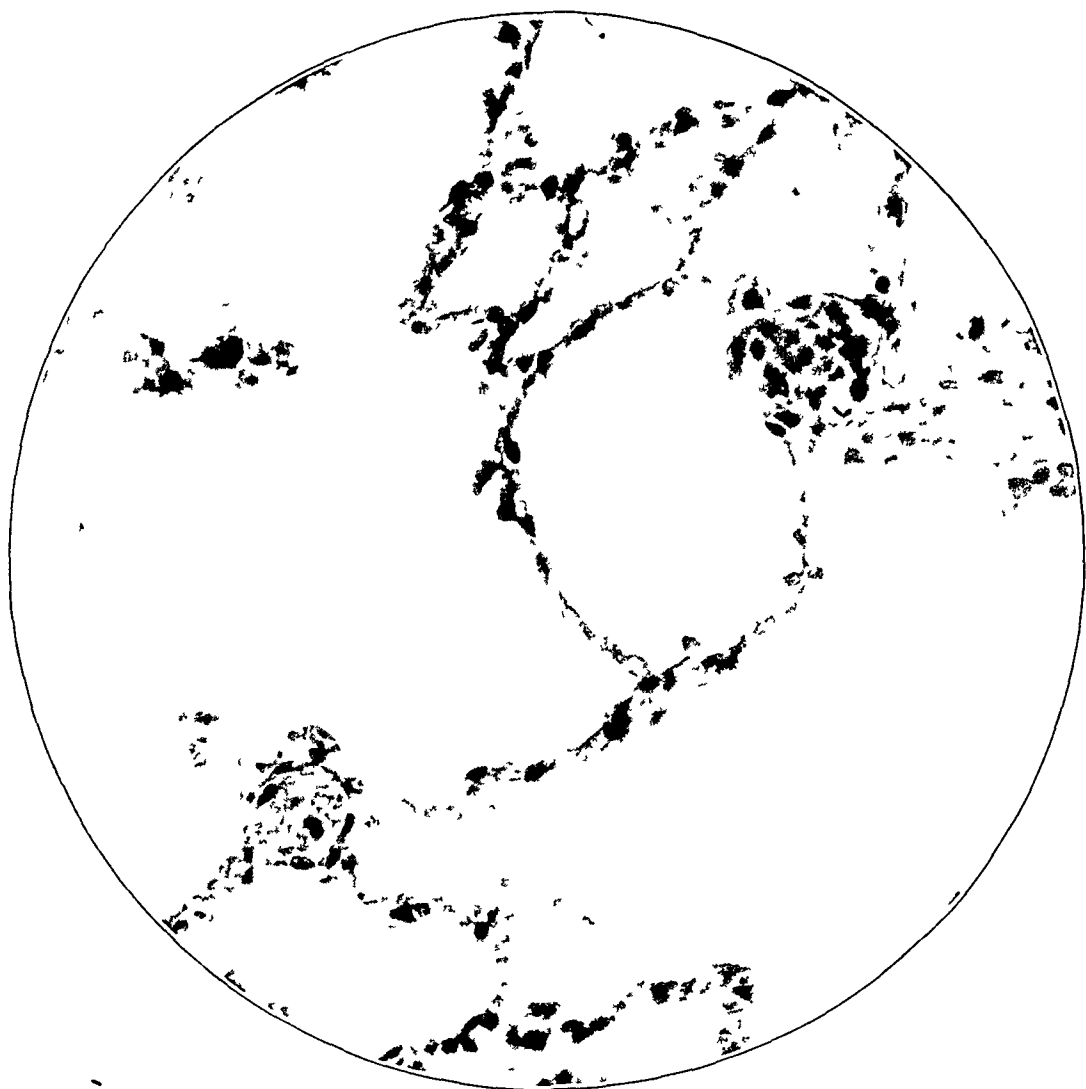


Fig 1—Section from portion of lung showing minimal amount of parenchymal damage Shows (1) emphysematous overdistension of alveoli, (2) congestion, (3) beginning extravasation of red blood cells into the alveoli, (4) two capillaries cut in cross section which are widely dilated and are occluded by blood platelet thrombi ($\times 400$)

opportunity obviously impossible in human beings And this opportunity has enabled us, we believe, to throw more light upon the pathogenesis of the disease

Materials employed—Four series of rabbits were inoculated intratracheally with the following materials

(1) Human nasopharyngeal washings In the first series, animals were inoculated with nasopharyngeal washings from early cases of

influenza These washings were obtained in the manner described elsewhere,¹¹ within twenty-four hours after the onset of the first symptoms of illness, and they were then carefully filtered under strict sterile precautions through Berkefeld filters size N or Mandler filters of corresponding density The filters were always tested with *B prodigiosus* The filtered nasopharyngeal washings were then cultured aerobically and anaerobically in ordinary laboratory mediums and found to be free of contaminations Inoculations were also made on the so-called chocolate agar medium in order to eliminate the possible presence of *B influenzae* of Pfeiffer or other hemoglobinophilic organisms From 1 to 3 c c of the clear filtrate were used for the intratracheal inoculations, the material being introduced in the manner subsequently to be described

(2) Filtrates of glycerolated lungs of inoculated animals In a second series, the injected material consisted of the lungs of animals in series one and three, which had been glycerolated for a variable period (from one week to fourteen months) and then filtered through Berkefeld or Mandler filters The lungs were removed in sterile fashion from the animals within from thirty-six to forty-eight hours after inoculation and were not further utilized unless found to be free of all secondary invading organisms Glycerolation was often employed as an added precaution as it did not seem to affect the virulence of the material appreciably

(3) Cultures of the punctiform bodies In the third series, the rabbits were inoculated intratracheally with cultures of the minute punctiform filtrable bodies isolated by Loewe and Zeman Most of the cultures were obtained from the filtered nasopharyngeal washings of early cases of influenza, persons in the first twenty-four or thirty-six hours of their illness Other cultures were derived from the lungs of animals which had originally been inoculated intratracheally with the filtered nasopharyngeal washings of early human cases of influenza And a third group of cultures employed was recovered from the lungs of animals in which the experimental disease had been produced by the inoculation of cultures isolated from such nasopharyngeal washings

One interesting feature of this third series of experiments is that the cultures of this filtrable virus, after being kept at incubator temperature for fourteen months, were not only found to be still viable, but also retained their unique pathogenic properties Similarly, the lungs of animals in which the disease had been produced by intratracheal inoculation of human nasopharyngeal washings could be preserved in 50 per cent glycerol, and after fourteen months the glycerolated material was viable and also retained an almost undiminished infectivity

(4) Control experiments The fourth series of experiments served as controls to series one, two and three The inoculated materials in this series consisted of the following

(a) Culture medium ascitic fluid containing kidney tissue and layered with petrolatum, which had not been inoculated but had been incubated at 37 C simultaneously with the inoculated cultures for varying periods of time up to fourteen months

(b) Berkefeld filtrates of glycerolated lungs of rabbits succumbing to intercurrent laboratory infections or to the intratracheal inoculation of various pyogenic organisms

(c) Filtrates of nasopharyngeal washings obtained in the customary manner from patients suffering with diseases other than influenza. Surgical cases were preferred to rule out possible contact infection

(d) Cultures of *Staphylococcus aureus*, *Streptococcus hemolyticus*, *Streptococcus anhemolyticus*, pneumococcus and *Bacillus bipolaris* (distemper)

(e) Cultures of *B. influenzae* of Pfeiffer which were derived from various sources such as (1) nasopharynx of normal individuals, (2) cerebrospinal fluid of influenzal meningitis, (3) nasopharynx, sputum and lungs of persons suffering from influenza during the pandemic ¹²

Technic of Inoculation—The rabbit, having been lightly anesthetized with ethyl chlorid,¹³ from 1 to 3 cc of culture or other material was inoculated intratracheally. In a few experiments this was accomplished by passing a fine rubber catheter into the trachea in the manner of the Meltzer-Auer method of intratracheal insufflation. It was found to be more satisfactory to inject the material directly through the tracheal wall by means of a fine needle and syringe, after previous removal of the hair with barium sulphide and sterilization of the skin with tincture of iodine ¹⁴. The animals immediately recovered from the very transient anesthesia and presented no evidence of any distress.

Symptoms of Illness—Often the first evidences of illness made their appearance within a few hours after the inoculation. Within twenty-four hours, the animals appeared to be severely ill, their movements were less active, breathing was more rapid, and the conjunctivae were injected. Over both sides of the chest, the stethoscope elicited numerous moist rales and, in some animals a distinct expiratory, asthma-like wheeze.

Leukopenia—Simultaneous with the development of these symptoms, there appeared a pronounced leukopenia, the number of leukocytes in the blood at times decreasing from 50 to 60 per cent within

12 For many of the strains we are indebted to Dr William H. Park of the Research Laboratory of the New York City Board of Health.

13 Ethyl chlorid was employed owing to the ease and rapidity with which a light anesthesia could be induced. It was proven that this volatile drug as used was incapable of producing any structural changes.

14 Direct intratracheal inoculation was performed with 18-gage needles connected to 5 c.c. Luer syringes. Entrance into the trachea was indicated by the easy withdrawal of air upon elevating the plunger of the syringe.

forty-eight hours The leukopenia was present in every instance after the inoculation of either active influ enza virus (filtered lungs or nasopharyngeal washings), or cultures obtained from the virus It was never encountered in animals inoculated with pyogenic organisms or with *B. influenzae* of Pfeiffer, on the contrary even the latter regularly induced a definite hyperleukocytosis

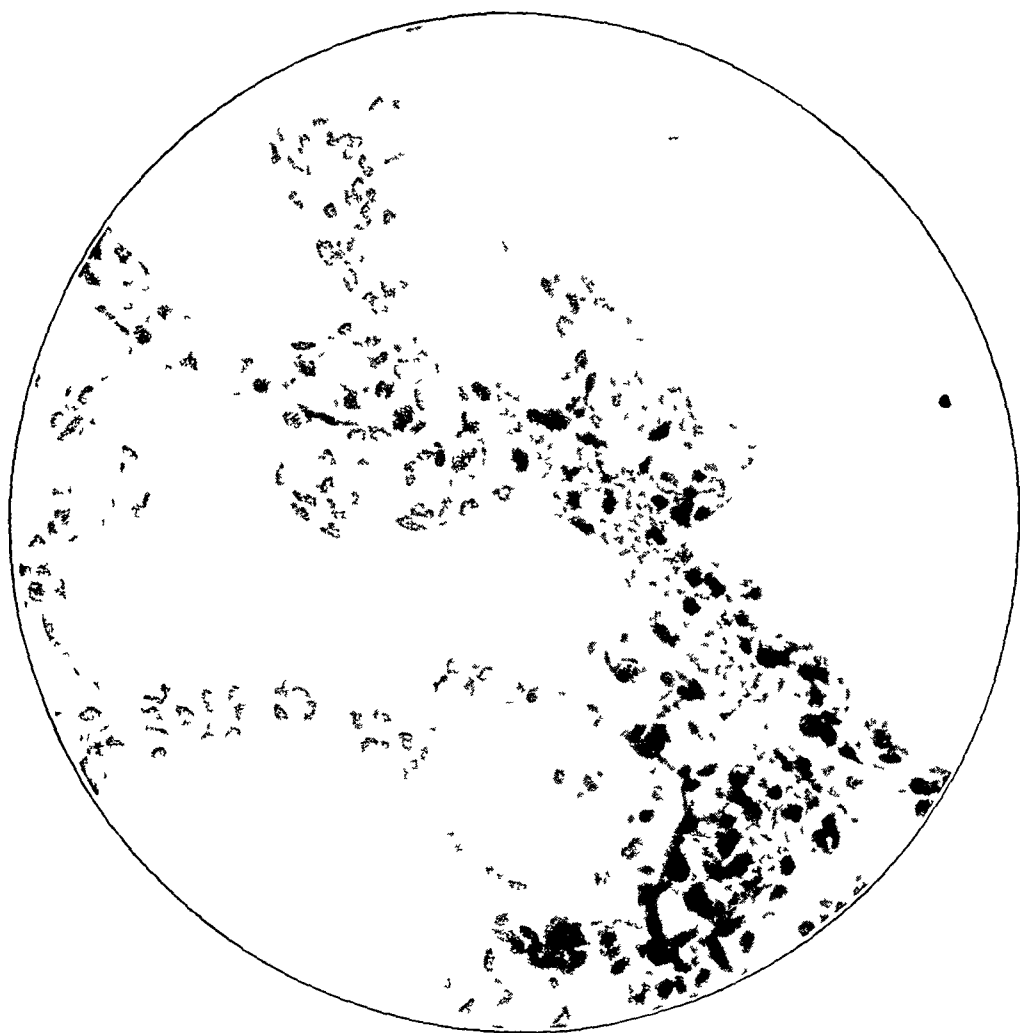


Fig 2—Section showing an occluded arteriole and its tributary capillaries cut longitudinally The outlines of the blood platelets comprising the thrombus can be made out, even with this magnification Although the thrombus contains a few polymorphonuclear and mononuclear leukocytes the cellular forms of inflammatory exudate are conspicuously absent in the alveolar air spaces and interalveolar tissue In this microscopic field the alveolar spaces contain serum and red blood cells, whereas in other portions of the same section the interstitial tissue is the more extensively infiltrated with the aplastic sero-sanguineous exudate ($\times 400$)

Secondary Invasion with Pyogenic Organisms—At the very beginning of the work, it was immediately observed that animals which were permitted to live longer than from forty-eight to seventy-two hours

after the onset of the disease usually developed various types of secondary infection within the damaged lung parenchyma. Exactly as in human influenza, the primary process then became obscured by complicating lesions such as pneumonic consolidations, abscesses, empyema, etc., from which various pyogenic organisms could be isolated. Simultaneous with the onset of this secondary bacterial invasion, the leukopenia rapidly gave way to a hyperleukocytosis.

It was therefore necessary to confine the study to the lungs of rabbits which were sacrificed¹⁵ within from twenty-four to forty-eight hours after the inoculation. The following observations therefore represent the earliest lesions of the experimental disease, at a time when cultures from the damaged lung were negative—except the filtrable organisms described by Olitsky and Gates and by Loewe and Zeman.

Gross Pathology—The lungs are usually voluminous and present a striking picture of acute emphysema. Although the process is often bilateral, usually one lung or parts of a lung are more extensively involved. The normal pale yellowish gray surface of the organ is mottled with deep pink in large diffuse areas. Here and there in these pink areas are small hemorrhagic foci, usually diffuse in outline.

A frothy edema fluid is often present in large quantity in the lumen of the trachea and larger bronchi. The mucous membrane of the latter regularly shows intense congestion and edematous swelling and is often stippled with minute hemorrhagic points.

On section of the lungs, no areas of firm consolidation are discoverable. The large pink areas appear to be chiefly the site of an intense congestion and edema, so that the cut surface drips a blood stained fluid. Within the confines of the pinkish lung tissue there are areas of swollen lung parenchyma of a deeper red which present the appearance of red jelly, but are compressible and moist. Often the affected portion of a lobe is a deep pink at the periphery, shading to a darker red at the hilus. In these red areas, some small dark hemorrhages, pinpoint to pinhead in size, are frequently discernable. Between the areas of involved parenchyma, the lung presents merely an intense emphysema.

Microscopic Picture—On microscopic examination, the salient feature of the pathologic process are (1) congestion and edema and occasional small hemorrhages in the tracheal mucosa, (2) small hemorrhages into the walls of bronchi and the presence of red blood cells in the bronchial lumen, (3) emphysematous overdistension of alveolar air spaces, (4) congestion, and in many places, edema of areas of lung parenchyma both interstitial and interalveolar, (5) hemorrhagic extra-

¹⁵ The animals were killed by a single sharp blow over the suboccipital region. Death was instantaneous.

vasations into the interstitial tissue of the alveolar walls with a great tendency for the hemorrhage to break into the alveolar air spaces, filling smaller or larger groups of them with red blood cells, (6) absence of ordinary cellular inflammatory exudate, (7) occlusion of numerous interalveolar and interstitial capillaries and arterioles by blood platelet thrombi. Except for the vascular lesions, all the other phenomena were also observed by Olitsky and Gates in their experimental animals

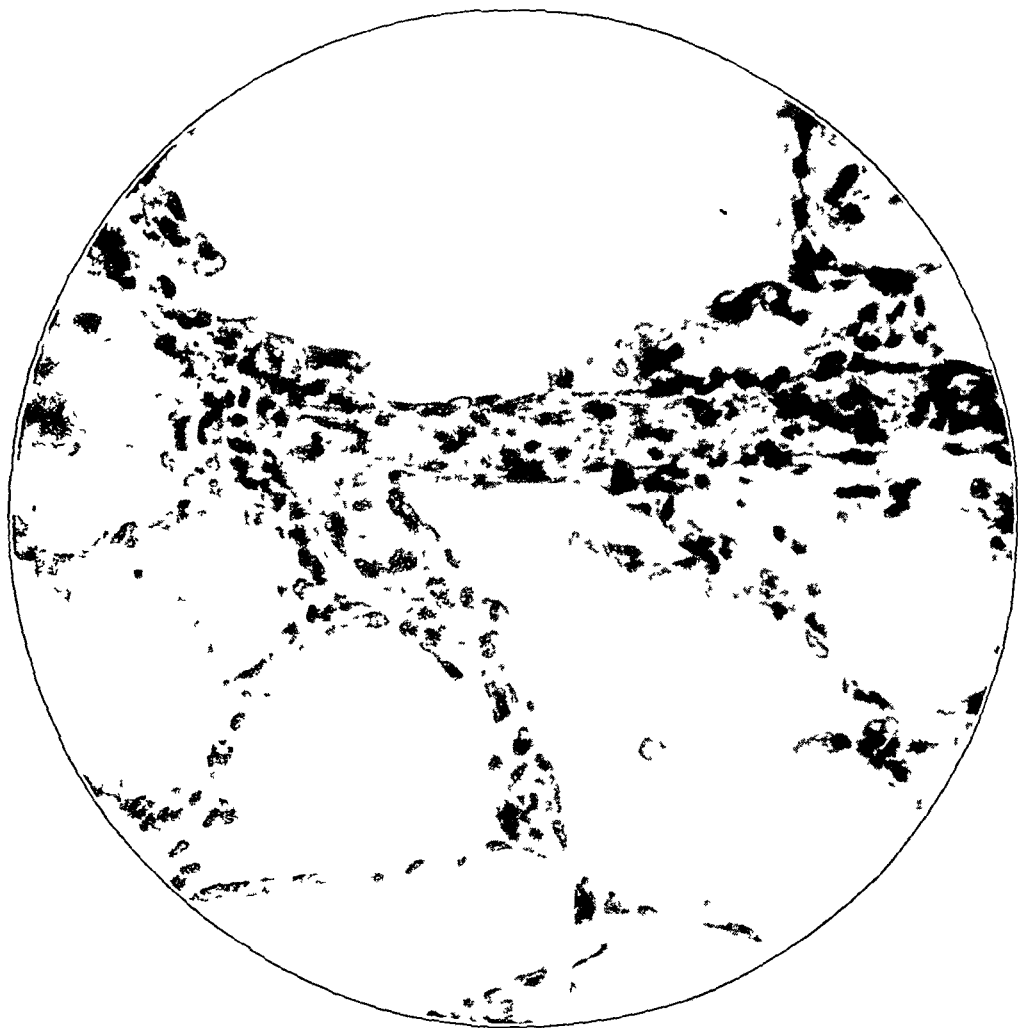


Fig 3—Section showing dilated and branching capillary occluded by blood platelet thrombus. The endothelial cells of the capillary wall are swollen and at several sites can be seen to have undergone proliferation ($\times 400$)

The changes in the tracheal and bronchial mucosa occur with great regularity. Similarly, the tendency to emphysematous overdistension of the alveolar air spaces seems to be a characteristic phase of the pathologic process. It is to be seen in parts of the lung parenchyma which show as yet no evidences of edema or of hemorrhagic extravasa-

tion It is not caused by the mechanical presence of the injected material within the respiratory tract, for by the time the first symptoms of illness appear in the inoculated animals (six or more hours after the injection) the inoculated fluid is undoubtedly entirely absorbed The cause is more likely to be the narrowing of the bronchial lumina due to congestion and edematous swelling of the lining mucosa The presence of the profuse frothy mucoserous fluid within the lumen of the bronchial tree, also probably contributes to the respiratory difficulty The development of these changes in the bronchi is coincident with the onset of asthma-like breathing and the presence of numerous moist râles on auscultation of the chest of affected animals

Congestion of the lung parenchyma is usually patchy in distribution, as is the edema In large and small areas, both the interalveolar tissue and the lumina of alveoli are filled with serum Similarly, the hemorrhagic extravasations are patchy in distribution and involve the interalveolar connective tissue as well as the lumina of alveoli These changes correspond with considerable accuracy to the lesions found in the lungs in the earliest human cases of influenza

Blood Platelet Capillary Thrombi—The minute intracapillary blood platelet thrombi constitute a significant and conspicuous feature of most of the experimental material that has thus far been studied They have been found in the lungs of animals that were killed shortly after the development of the first manifestation of illness, and probably precede and are in part responsible for some of the features of the pathologic picture

The occluded capillary loops are always widely dilated, the lining endothelium is swollen and often shows beginning proliferations, the lumen is occupied by a mass of blood platelets, scattered through which are sometimes a variable number of mononuclear and polymorphonuclear leukocytes In the vicinity of such an obstructed capillary or minute arteriole, either edema or interstitial and intra-alveolar hemorrhages are usually present But similar changes can sometimes be seen in capillaries within areas of lung parenchyma which show as yet merely some interstitial congestion and emphysema The lesion has also been seen in the mucous membrane of the trachea of these animals

Emulsions and filtrates of the lungs of animals showing such lesions have induced the experimental disease when injected into the trachea of other animals The virus has thus been passed in series through several transmissions and in each transmission the capillary lesions have been seen They, therefore, probably represent an essential and characteristic feature of the pathologic process in the earliest stages of experimental influenza

Absence of Characteristic Lesions in Control Animals—This belief is strengthened by the fact that we have not encountered this lesion of the lung capillaries in an extensive experience with human and animal pulmonary diseases. We have repeatedly produced pulmonary infections in rabbits by the intratracheal inoculation of various common pyogenic organisms such as the *Staphylococcus aureus*, *Streptococcus*

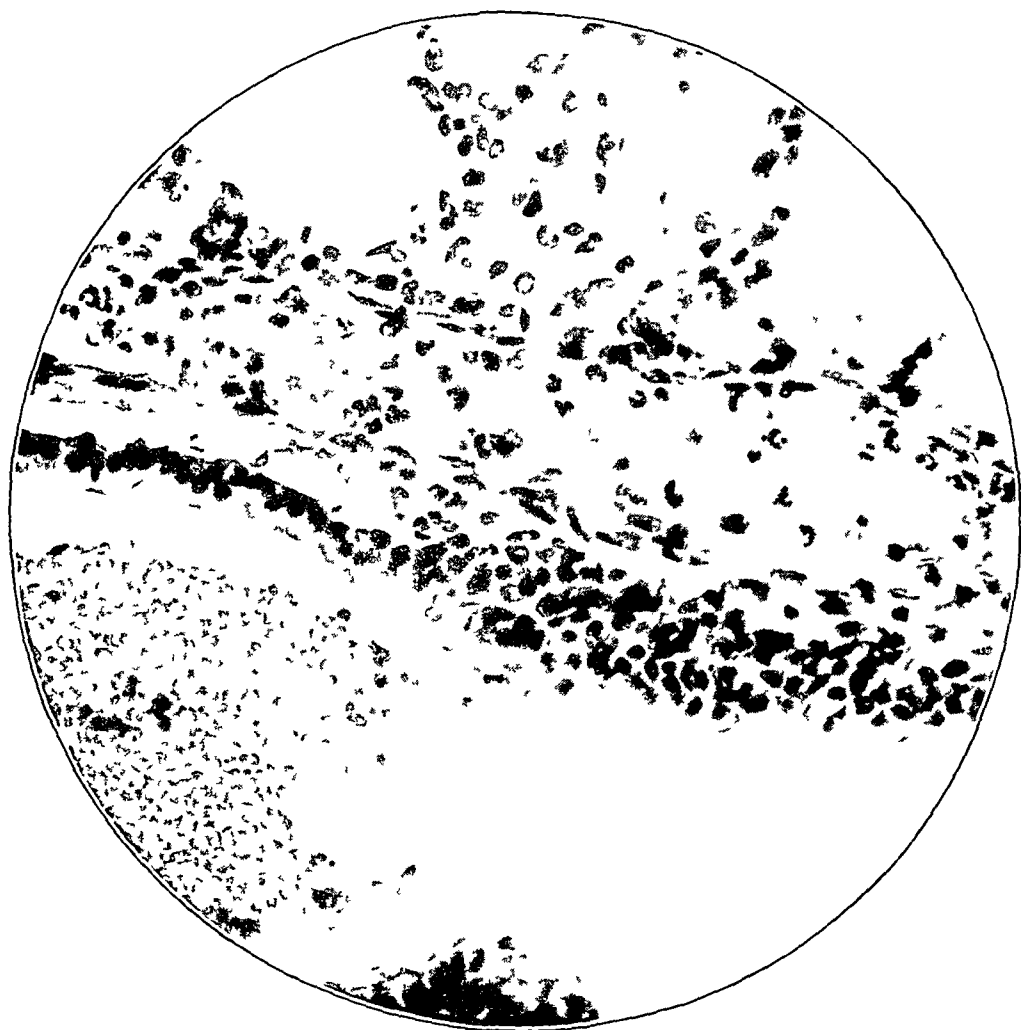


Fig 4—Peribronchial arteriole. The lumen of the small bronchus, which occupies the lower half of the field, is filled with red blood cells. The adjacent arteriole which runs parallel to the long axis of the bronchus, is occluded with a blood platelet thrombus containing scattered polymorphonuclear leukocytes. The endothelium lining the arteriole, more especially on the side adjacent to the bronchioles, is very evidently in the process of proliferation ($\times 400$)

hemolyticus, pneumococcus, *Bacillus bipolaris* (distemper) and the *B influenzae* of Pfeiffer, and have never seen anything remotely suggesting it.

Neither the capillary thrombi nor any of the other features of the experimental disease could be produced by the intratracheal injection of uninoculated culture material. In order to eliminate the possi-

bility that the pulmonary changes in our experimental animals might be due to a purely chemical action of the injected ingredients, the control culture mediums were employed after incubation at 37 C for variable periods of time up to fourteen months

Significance of the Blood Platelet Capillary Thrombi—Changes similar to those seen in capillaries and arterioles in our animal lungs have also been described in the earliest stages of human influenza by Glaus and Fritzsche, Siegmund, Winternitz and Klotz. They have been searched for, though not found, by Marchand, Oberndorfer, Dietrich, Koopman and others who have also studied early examples of the disease. This may, in part, be due to the fact that in their human material the stage of secondary infection had already begun with its consequent obscuring of the primary pathologic lesions. It is more probable, however, that the greater frequency with which the capillary blood platelet thrombi occur in our experimental material is due to the fact that a much greater concentration of virus is introduced into the respiratory passages of the experimental animal than is responsible for infection in human beings.

As a result of a pathologic study of two fulminating cases of the disease, Oberndorfer was the first to voice the belief that the influenza virus produced a primary damage on the intima of small vessels. A similar viewpoint, based on a study of human material, has been expressed by Dietrich, Winternitz, Klotz, Glaus and Fritzsche and Soerenson.

The lesions which we have been able to produce experimentally by means of influenza filtrates and influenza cultures leave little room for doubt that the virus possesses a peculiar affinity for the vascular endothelium. Numerous short stretches of capillaries and arterioles become widely dilated, apparently due to a complete loss in their normal tonus—and through their walls there occurs a great exudation of serum or a simultaneous extravasation of serum and red blood cells, which fills the interlobular and interalveolar connective tissue spaces and the alveoli in more or less sharply limited areas of vascular distribution. The blood platelet thrombi which become deposited in some of these dilated and damaged capillaries and arterioles are also to be encountered occasionally in parenchyma which is not as yet involved in any serous or hemorrhagic extravasation, so that they undoubtedly also represent an expression of the primary damage to the vascular endothelium. They are certainly not secondary to the other parenchymal changes.

Winternitz laid especial emphasis on the frequency with which necrosis of interalveolar septa occurs, and he regarded it as one of the characteristic effects of the disease. In the experimental material, necrosis and even rupture of interalveolar septum was occasionally encountered, but at the stage of the process at which the study was

necessarily made, this was not as yet a wide spread or conspicuous phase of the pathologic picture. In one of the fulminating cases of Glaus and Fritzsche, which probably represented a stage of the process somewhat later than our experimental disease, they call attention to the fact that though the necroses are numerous, the capillary thrombi are also to be seen outside of the necrotic areas. "In many instances," they state, "one can observe how the necrosis occurs in the immediate proximity of these thrombosed vessels." The experimental observations confirm this viewpoint that the capillary thromboses precede the necrosis and are not secondary to it.

Aplastic Character of the Inflammatory Exudate — Perhaps the most striking feature of the microscopic picture in our experimental material and one which alone serves to differentiate it from any other type of pulmonary inflammatory process is the aplastic character of the alveolar as well as interstitial exudate. An occasional proliferated endothelial cell is encountered. But unlike any other type of pulmonary infection, no polymorphonuclear or other leukocytes are seen in the early stage of the process. The exudate consists almost wholly of serum or of serum and red cells. Although other pathologists have noted this unique feature of the process in early uncomplicated human influenza, Winternitz and his co-workers have especially emphasized the observation that "in the early stage, one of the most outstanding features is the absence of polymorphonuclear leukocytes in the reactionary process."

As soon as the secondary bacterial invasion occurs, an extensive leukocytic invasion rapidly changes this phenomenon and thereby completely obliterates the specific features of the pathologic picture. In the experimental animals such a transformation was observed to occur as early as forty-eight hours after the onset of the disease.

Yet even before this occurs, polymorphonuclear leukocytes are encountered in abnormal numbers within the blood platelet capillary thrombi. At a time when the alveolar and interstitial exudate, except for red cells, is still absolutely aplastic, many of the thrombi in occluded capillaries and arterioles are seen to be invaded by occasional proliferated endothelial cells and by polynuclear leukocytes in fair numbers. The aplastic nature of the other parenchymal changes would indicate that the virus of influenza does not possess the slightest chemotactic property. The appearance of leukocytes only within the capillary thrombi is, therefore, probably initiated by the positive chemotaxis exerted by the presence of the damaged endothelium within these vessels. In fact, their occurrence solely in the occluded vessels is evidence that damage has occurred at these sites and indicates that this damage, and not mere mechanical factors, is responsible for the blood platelet deposition.

Winternitz, Wason and MacNamara described a homogeneous hyaline-like necrosis of the epithelium lining the trachea and bronchi, and, mainly for this reason, they likened the pathologic picture of the disease to that produced by the poisonous gases employed during the war. We have failed to observe this superficial necrosis in our experimental material, as have most other pathologists in their early examples of human influenza. Therefore, we feel that it is probably caused by a combination of the primary damage to the mucosa and the secondary infection and that it represents a complication rather than an essential feature of the primary pathologic process.

SUMMARY

The following pulmonary lesions were produced in rabbits by the intratracheal inoculation of Berkefeld filtrates of nasopharyngeal washings from early cases of influenza or of cultures of the filtrable punctiform bodies cultivated from such washings by Loewe and Zeman.

(1) Congestion, edema and small hemorrhages in the mucous membrane of the trachea and bronchi.

(2) Presence of a profuse, slightly blood-tinged, frothy, serous fluid in the lumen of the bronchi.

(3) Diffuse patchy distribution of red, jelly-like lesions throughout the lungs.

(4) Intense congestion of a large part of the intervening lung parenchyma and acute emphysematous overdistension of alveoli.

(5) Widespread exudation of serum and extravasation of red blood cells from the vessels, filling interstitial tissues and groups of alveolar air spaces.

(6) Aplastic character of this exudate.

(7) Aneurysmal dilatation of short stretches of capillaries and arterioles and sometimes closure of the lumen of these vessels at these sites by blood platelet thrombi.

(8) Tendency to early secondary invasion with pyogenic organisms, which then induce a rapid purulent infiltration, thereby completely obliterating the primary and specific picture of the disease.

These characteristics have all been observed in human influenza by pathologists who have had the opportunity to study the lungs of patients with fulminating disease who died within the first few days of their illness and before secondary infection had occurred. The lesions as they occurred in these early cases have been regarded as constituting a specific pathologic picture. Our experimental lesions correspond with considerable accuracy to those of human influenza and they cannot be confused with the changes produced by any other pathogenic organism either in human beings or in animals.

The unusual nature of the pathologic process in influenza is apparently due to the fact that the virus of this disease possesses a remarkable affinity for the vascular endothelium. The virus gains access via the respiratory passages, and is rapidly absorbed through the mucous membrane of the trachea, bronchi and bronchioles. Apparently, as a result of its peculiar endotheliotoxic property, it then rapidly calls forth a profuse outpouring of serum and red blood cells in patchy areas throughout the lungs.

Further evidence of this vascular damage is to be seen in the complete loss of tonus in many capillary loops and in the early occlusion of many capillaries and minute arterioles by blood platelet thrombi. This phenomenon, though observed in the lungs of some of the earliest human cases of influenza that were studied pathologically, can be regularly produced experimentally with influenza virus and influenza cultures and is of considerable pathogenetic significance.

THE MECHANISM OF THE DEVELOPMENT OF NON-BACTERIAL, CHRONIC CARDIOVALVULAR DISEASE¹

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A fairly complete search through the literature reveals no accurate knowledge or satisfactory explanation of the pathologic process which is the basis of the progressive development of chronic cardiovalvular disease. By chronic cardiovalvular disease is meant a chronic, non-bacterial, nonrheumatic disease of a heart valve, or of valves, which is characterized at the necropsy by marked fibrosis of the valve cusps or flaps sometimes causing marked distortion or stenosis, at times with calcareous deposit in the valves, but unaccompanied by vegetations other than very small ones, such as are described in this paper.

The histologic changes in simple or verrucous endocarditis are well known, as are those of the terminal stage of the process which is usually, though improperly, termed "chronic endocarditis." The cause of the progressive changes in nonbacterial lesions of the heart valve, and the mechanism of these changes, is very imperfectly understood.

It will be necessary, before taking up this problem, to discuss the terminology and classification of acute and chronic diseases of the heart valves. Many of the older terms given to different types of cardiac disease have been found inappropriate in the light of recent knowledge. Many cases have erroneously been termed acute endocarditis where there was no acute inflammation of the endocardium. The term, however, which probably has been most abused is "chronic" endocarditis. This term should be discarded, as there is in all probability no disease of the heart valve which can be described as a "chronic" inflammation. The only conditions that should be termed endocarditis are those which are inflammatory in nature, and in which the etiology of the inflammatory lesion of the endocardium is known. These are bacterial, rheumatic and syphilitic endocarditis. As Libman suggests, the organism causing the bacterial endocarditis should always be included in the name of the lesion, such as "acute *Staphylococcus aureus* endocarditis."

In the same way, "chronic myocarditis" is usually improperly applied. Chronic inflammation of the myocardium is very rare, indeed. Most cases termed "chronic myocarditis" are conditions entirely different from this, such as myocardial weakness, interstitial fibrosis of the myocardium, either localized or diffuse, coronary artery disease, etc.

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Libman¹ differentiates sharply between cases of valvular defect alone and cases of endocarditis occurring with or without a previous valvular disease. He describes a valvular defect as "a direct result of a previous disease process of the valve." The important point to be made clear is that a valvular defect is the result, or sometimes the end stage, of disease of a heart valve, and cannot, in any sense, be termed an endocarditis, acute or chronic. Libman tabulates the causes of valvular defects as follows:

- 1 Rheumatic endocarditis
- 2 Syphilitic endocarditis
- 3 Atherosclerosis
- 4 Congenital defects
- 5 Traumatic lesions
- 6 A previous bacterial infection, with recovery

He classifies the varieties of "endocarditis" (not valvular defects) as follows:

- 1 Rheumatic
- 2 Syphilitic
- 3 Bacterial
- 4 Terminal (verrucous)
- 5 Indeterminate

This terminology and classification is considered the best yet suggested. It is believed, however, that the term "endocarditis" should be eliminated entirely, and, in its place, the conditions should be termed acute or chronic cardiovalvular disease. It is probably too much to expect that the term endocarditis will be given up, but it seems certain that the term chronic endocarditis will be dropped. The term endocarditis is used herewith in connection with rheumatic fever and bacterial valvular disease, in order to conform with the present accepted terminology.

We are not concerned in this paper with bacterial infections of the endocardium, whether they are acute or subacute, or, as the latter is sometimes termed, chronic malignant endocarditis. These conditions have been described well by Schottmueller, Horder, Osler, Libman, Rosenow and others. The mechanism of the development of these lesions is also well understood, whether considered as starting from a bacterial embolus in the valve, or whether they start from bacterial implantation on the valve. Some phases of this mechanism, however, will be discussed later, as they have a bearing on the mechanism of the development of chronic cardiovalvular disease.

¹ Libman, E. A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, *Am J M Sc* **144** 313, 1912. The Clinical Features of Cases of Subacute Bacterial Endocarditis That Have Spontaneously Become Bacteria-Free, *Am J M Sc* **146** 625, 1913. Some General Considerations Concerning Affections of the Valves of the Heart (Clinic of Dr. E. Libman, Mount Sinai Hospital, New York.)



Fig 1—Verruca on mitral valve in a case of acute rheumatic fever, showing beginning organization of hyaline thrombus deposit and reaction in valve beneath

Our problem narrows itself to this in what manner do chronic n n bacterial diseases of the heart develop, and what is the pathology and histology of this process? It is believed that the clue to the solution of this problem is to be found in the correlation of the results of the study of certain small excrescences found in a number of abnormal or diseased conditions of the heart at different locations on the endocardium, but most often on the valves. These conditions are congenital cardiac disease, so-called simple or verrucous endocarditis of rheumatic fever, so-called terminal verrucous endocarditis, and verrucous endocarditis in practically all cases of chronic cardiovalvular disease. These will have to be described separately, and it is also necessary to discuss bacterial endocarditis.

VARIETIES OF ENDOCARDITIS

Bacterial Endocarditis—The macroscopic and microscopic characteristics of bacterial endocarditis are well known and need no further description. Reference can be made, in particular, to the articles of Libman.¹

The vegetations, except in acute fulminating cases, are comparatively large and rough, being warty or cauliflower-like in appearance, or occurring as even larger, irregular masses. In cases such as acute pneumococcus endocarditis complicating a pneumonia, the vegetations may occasionally be small and beaded, smooth and glistening. The organism causing the lesion always can be demonstrated readily, however, in either smear, culture or section, thereby differentiating these cases from the verruc  of acute rheumatic endocarditis.

In only a single group of bacterial endocarditis cases, namely, the bacteria free cases of subacute bacterial endocarditis, as described by Libman, are no bacteria found in the vegetations. Nevertheless, there can be no doubt that Libman has demonstrated that bacteria caused the lesions and these subsequently become bacteria free.

Bacterial vegetations are always friable, unless calcified, and even then, they are usually friable. They are made up of masses of blood platelet thrombus, mixed thrombus, bacteria scattered or in masses, and also sometimes of calcareous deposit. Degeneration or necrosis of the thrombus material often occurs. Organization takes place only to a slight or moderate extent at the base of the vegetation, except in Libman's bacteria free cases, where it may extend throughout the vegetation. In all other bacterial cases the surface of the vegetations is not covered by endothelium and it is usually not covered even in the bacteria free cases. Bacteria growing in the thrombus form almost the entire surface layer but the bacteria may also be found far beneath the surface.

Occasionally small beaded vegetations occur alongside of large ones in subacute bacterial endocarditis which, if alone, might be confused



Fig 2—Verruca on mitral valve in a case of acute rheumatic fever. Larger than the one shown in Figure 1.

macroscopically with acute rheumatic endocarditis. Microscopically, they are easily differentiated, as they always contain bacteria. Bacterial vegetations, therefore, are merely infected thrombi on the valves.

Simple or Verrucous Endocarditis of Rheumatic Fever—This condition is so well described by Aschoff in his textbook on Pathology, that only the necessities of this article justify personal observations of this lesion. This lesion is distinctive. The gross lesion is sufficiently characteristic so that acute rheumatic fever, or one of its associated conditions (such as chorea), can be diagnosed in practically every case in which this lesion is found. In a few hearts lesions have been observed that were so similar to those of verrucous rheumatic endocarditis that macroscopically it could not be decided definitely whether they were the lesions of rheumatic fever. In all of these cases, when a positive opinion could not be formed, subsequent study of the heart failed to reveal Aschoff bodies, which are the specific, microscopic, myocardial lesions of acute rheumatic fever and its allied conditions. In all hearts which were macroscopically regarded as representing a verrucous endocarditis of rheumatic fever, Aschoff bodies were found in the myocardium.

Rheumatic verrucous endocarditis appears grossly as a beaded line along the line of closure of the various valves. These beads vary in size from being barely visible to 2 or 3 mm. in both width and height. They may be either discrete or fused. When fused they form a continuous line on one or more of the valve flaps or cusps. When the beads are very small they give the line of closure of the valve a sandpaper-like appearance. The lesions are either colorless, or grayish white, rounded, smooth and glistening. They are never pedunculated but are always sessile. The verruæ are rather firm and tough, are not easily broken off from the valve and when picked off, a small portion of the superficial tissue of the valve invariably comes off with them.

MICROSCOPIC APPEARANCE The minute, beaded vegetations are composed entirely of an organizing, hyaline thrombus. The connective tissue immediately beneath the endocardium furnishes fibroblasts through which the thrombus becomes organized. The process of organization can, therefore, be regarded as beginning in these tissue cells. This area of actively growing connective tissue cells has all the characteristics of growing connective tissue elsewhere. More plasma is present between these cells than is found elsewhere in the valve. The valve about the base of the thrombus and, at times, the tissue throughout the valve, shows an inflammatory process. This process is an infiltration with mononuclear leukocytes, occasional plasma cells and polymorphonuclear leukocytes. The endothelium on either side of the thrombus, where it arises from the endocardium, shows a condition of active growth. There is apparently an effort on the part of the endothelium to



Fig 3—Terminal verrucous endocarditis, mitral valve, no organization of hyaline thrombus deposit and no reaction in the valve beneath it

grow up over the thrombus. This new endothelium usually extends up on either side to a distance of from one-fourth to one-third of the surface of the thrombus. The verrucæ in the acute stage are infrequently completely covered by endothelium, though this always occurs with the older lesions. This observation is at variance with that of Libman, who claims that the endothelium rapidly grows over and completely covers the small verrucous vegetations.

In different vegetations may be observed varying numbers of hyaline thrombi encroached on by granulation tissue. Growing into the thrombus from its base, and from its side, the fibroblasts then attack these islands from their entire periphery and eventually convert them into a ball or whorl of granulation tissues, which become incorporated in the valve. This has an important bearing on observations which will be reported on later.

A careful search has been made by Rothschild and Thalhimer for bacteria and protozoa in the vegetations and myocardium in many cases of acute rheumatic fever. In no instance were any bacteria or protozoa found. It may also be stated here that no organisms were ever found in Aschoff bodies. This observation is of importance in relation to the contention of some authors that rheumatic fever is caused by a special type of streptococcus.

It could not be determined positively whether the minute thrombi of the vegetations were secondary to a lesion of the endothelial layer of the endocardium, or of the subendothelial layer. Beneath the very small lesions changes are present only in the most superficial layer of the endocardium. These changes are so superficial that they seem to indicate that the primary lesions are essentially endothelial and not sub-endothelial.

It is of interest to note that Aschoff bodies,² or Aschoff cells, were never found in the vegetations, in their base or in the valves. Attention should be called to the fact that emboli never arises from the vegetations in cases of acute rheumatic endocarditis, since the vegetations are never friable enough to break and form emboli. Where embolic phenomena occur in this condition the emboli must arise from thrombi situated elsewhere than on the heart valves, such as from an auricular thrombus.

Terminal Verrucous "Endocarditis"—Terminal verrucous "endocarditis" occurs in patients who die after a long, slowly progressing illness, such as carcinoma, tuberculosis, etc.

² In a study made by Rothschild and myself (Rothschild, M. A., and Thalhimer, W. On the Significance of the Sub-Miliary Myocardial Nodules of Aschoff in Rheumatic Fever, *J. Exper. M.* **19** 417, 1914), a very careful search was made in the valves of rheumatic hearts for Aschoff bodies. We were, and are still, at a loss to explain their absence here and their presence in the specific lesions of the myocardium.

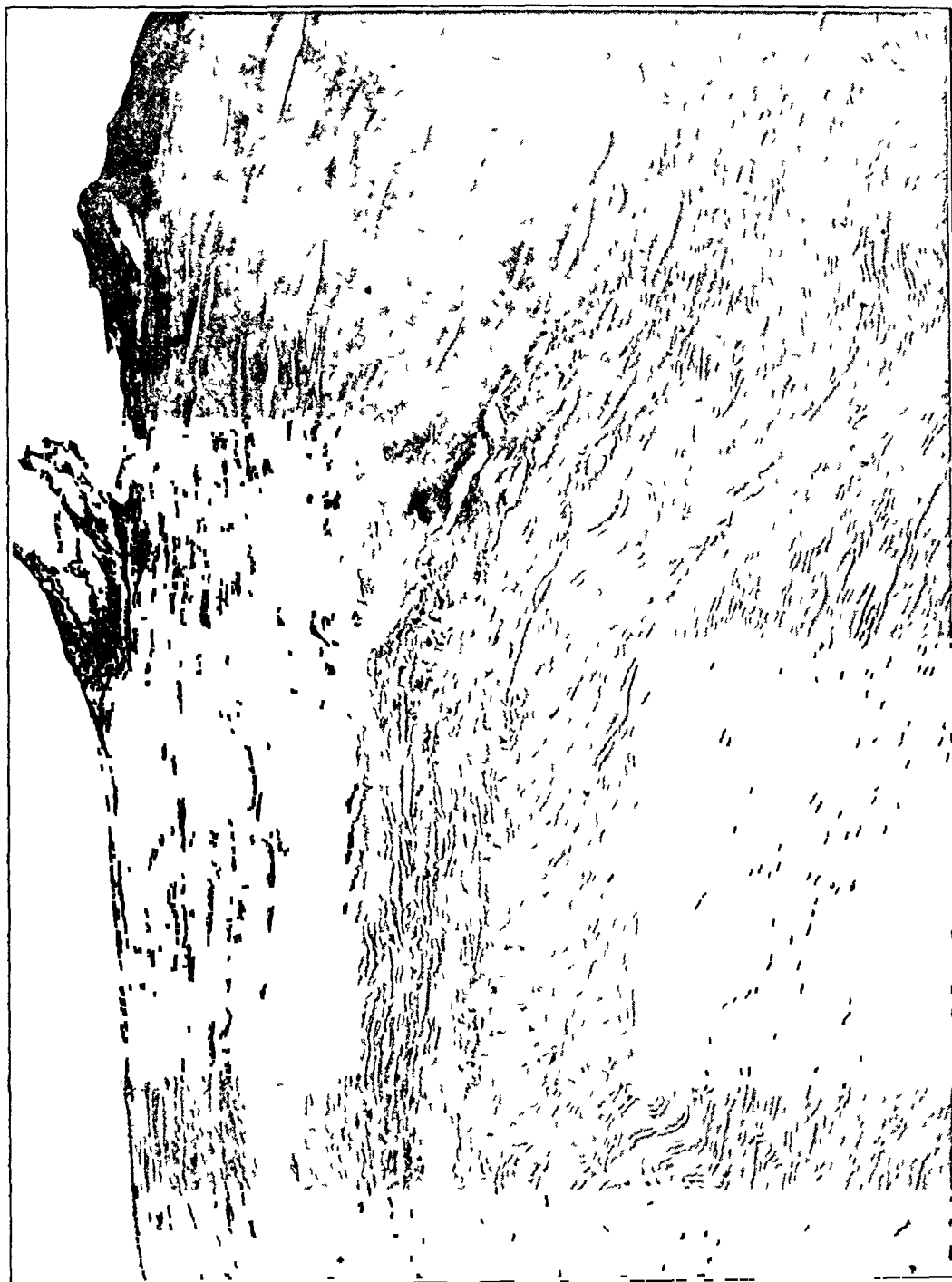


Fig 4—Terminal verrucous endocarditis, flat hyaline thrombus deposit on aortic valve. No organization of thrombus or reaction in the valve beneath it.

There are present upon the heart valves of many of these cases very minute, colorless or gray, rounded, glistening, firm verrucæ. They are usually smaller than those in rheumatic fever, fewer in number, scattered, and never form a continuous beaded line.

Microscopically these terminal verrucæ have identically the same structure as those caused by rheumatic fever, but there is no inflammatory reaction in the valve, either near the verrucæ or elsewhere. The small vegetations are formed entirely of hyaline thrombi, usually bare, but sometimes covered partially or even completely by endothelium. Either no organization of this thrombus is present, or practically none. There is no change in the valve beneath the verrucæ which is in any way related to the process on the surface of the valve. The small vegetative lesions have all the appearances of a recent process, without any accompanying inflammatory changes and with only proliferative changes in the heart valve.

A Special Type of Verrucous Endocarditis Found on the Valves of Nonbacterial, Nonrheumatic Chronic Cardiovalvular Disease—Verrucous "endocarditis" in chronic cardiovalvular disease is believed to be of common occurrence and yet seems to have been either comparatively unnoticed, or regarded as unimportant. I call attention to these lesions in the hope that others will verify the fact of their common occurrence and of certain structural valve changes associated with them.

On practically all thickened, fibrosed valves, careful inspection will reveal the presence of few or many minute verrucæ, grossly and microscopically similar in appearance to the very small lesions of terminal verrucous endocarditis. They are specially common on valves presenting marked stenosis, such as "buttonhole" mitral stenosis. In these extreme degrees of valvular defect the valve flaps are greatly thickened, very fibrous, usually uneven and often infiltrated with small or large amounts of calcium. Very often one or both places of junction of the two mitral flaps have a superficial, or deep, cracklike defect, which has somewhat the appearance of an ulcer. These cracks are at the ends of the "buttonhole" opening in the valve. The edge of these ulcer-like lesions is firm, irregular and slightly raised. The bases are rough and dull in appearance, as though composed of poorly nourished or degenerative tissues. On or near the edge of the cracks, as well as on the rounded valve edges, are found a few, or many small verrucæ. These verrucous lesions in their macroscopic and microscopic appearance resemble both rheumatic endocardial verrucæ and terminal endocardial verrucæ, and have some of the characteristics of both. They are generally larger than the terminal, but not as large as the rheumatic lesions. They also are composed of hyaline thrombi usually bare, but sometimes covered by endothelium. They show different degrees of



Fig 5—Small flat verruca on mitral valve in a case of chronic cardio-valvular disease. Organization is occurring and fibroblasts are scattered throughout the hyaline thrombus mass. The surface is covered by endothelium.

organization, from a small amount up to complete fibrosis. A slight or moderate grade of mononuclear cellular infiltration is quite constantly present at the base of the vegetation. This may be present elsewhere in the valve, but usually is not.

The more organized verrucæ very often revealed a whorllike arrangement of the newly formed connective tissue and some of the completely organized verrucæ are made up of very dense fibrous tissue, with few flattened, densely staining nuclei. Areas of hyalin (possibly thrombus) are found in some of the verrucæ. Microscopically the structure of the valves is seen to be made up of dense, irregularly arranged fibrous tissue. The dense fibers of this tissue are, in general, parallel to the valve surfaces, but a wavy or even a whorllike arrangement of the fibers is often present. These whorls are found with special frequency in flattened knoblike projections of the valves near the verrucæ, and seem to be the result of the manner of organization of the verrucæ. The central portion of the valve often contains areas of hyaline degeneration.

The cracks mentioned above are bare of endothelium, which stops at the edge. The base is made up of the fibrous tissue of the valve, with a layer of superficial degeneration, and here and there, small bits of hyaline thrombus. A considerable degree of calcareous deposit is usually present along the edge and in the base of the crack.

Nonbacterial Endocardial Vegetations in Congenitally Abnormal Hearts—It is recognized that "endocarditis" commonly develops on valves of congenitally abnormal hearts. Necropsies have been performed in many of these cases and the cardiac abnormalities and gross appearance of the valves have been described carefully. Unfortunately, the microscopic structure of the valve lesions has seldom been studied. Bacteriologic investigations either have not been done at all, or have been unsatisfactory. Sufficient care has not been taken to rule out post-mortem invaders of the heart's blood when positive postmortem bacterial cultures were obtained. Very few cases were studied clinically by means of blood cultures. Many of the important and most often quoted cases came to necropsy previous to, or during the early years of, the development of the science of bacteriology.

Nevertheless, quite a number of cases of "congenital heart disease" are recorded in the literature in which it has been proved that a superimposed acute or subacute bacterial endocarditis occurred. The heart valves have usually shown a chronic thickening and bacterial vegetative process. This fact directs attention to well known observations which are of importance. One is, that the valves of congenitally abnormal hearts are prone to become thickened and fibrosed. The other is that these compromised valves are susceptible to bacterial infections, just as is the case with all chronically diseased heart valves.



Fig 6—Verruca on mitral valve in a case of chronic cardiovalvular disease. Organization is almost complete, only two small unorganized areas of hyaline thrombus remain. The newly formed connective tissue has a whorllike arrangement. The surface is almost completely covered by endothelium. The vegetation is flattened and almost completely incorporated into the valve.

Attention can now be directed to certain organic changes in congenitally abnormal hearts and also to some personal observations of these changes

A number of cases are on record in which endocardial thickening, or thickening of the intima of the large arteries which arise from the heart, has been observed at situations where abnormalities in the course of the blood stream through the heart have caused this stream to impinge on the endocardium or intima, or to put unusual strain on it. These thickenings have also occurred at places where slowing of the blood stream, or eddies in it, have occurred. Bacterial endocarditis has also been found at these situations. Illustrations of this are lesions (bacterial or nonbacterial) in the pulmonary artery opposite an open ductus arteriosus where the blood has impinged, or around the pulmonary opening of the ductus where the stream has been slowed and thrown into eddies.

In addition, I have had the opportunity to study several congenitally abnormal hearts where nonbacterial vegetative lesions were present on the valves.³ To avoid repetition of what has gone before—the lesions bear a striking resemblance macroscopically and microscopically to the verrucæ of rheumatic endocarditis, terminal endocarditis and those observed on chronically diseased valves.

PRELIMINARY SUMMARY

The nonbacterial vegetations on the heart valves which have been described are formed of small thrombi on the valve. These lesions are verrucous rheumatic endocarditis, terminal verrucous "endocarditis" verrucæ on chronically diseased valves, and nonbacterial vegetations on the valves of congenitally abnormal hearts. It is believed that the same conditions which govern thrombus formation in blood vessels govern the formation of a thrombus on a heart valve. The underlying factors in thrombus formation are not understood perfectly, but a great deal of investigation of the condition has been made and the summation of our knowledge of the subject is best given in the conclusions arrived at by Aschoff.⁴

So we see from all these experiments that the slowing of the blood stream and the alteration of the blood elements themselves, especially alterations of the platelets, are the chief factors in the production, not only of the static, but of toxic thrombosis, so far as we are concerned with thrombus formation in the flowing blood stream. In static and similar types of thrombi the slowing of the blood stream is of primary importance, while for the toxic varieties the changes in the blood elements have the dominating influence.

³ One of these cases has been quoted in Dr. Abbot's article on Congenital Heart Disease, in Osler's System of Medicine.

⁴ Aschoff, L., von Beck, B., and de la Camp, O. *Beitrag zur Thrombosefrage*, Leipzig, Verlag von F. E. W. Vogel, 1912.



Fig 7—Chronic cardiovalvular disease Whorls occur in the fibrous tissue of the aortic valve

The different types of chronic cardiovalvular disease and aseptic vegetations will be taken up separately, and a theory of the cause, development and end result will be advanced

PROPOSED EXPLANATION OF MECHANISM OF DEVELOPMENT OF DIFFERENT TYPES OF CHRONIC CARIOVALVULAR LESIONS

Verruccous Rheumatic Endocarditis—There is sufficient evidence of inflammation in the heart valve first, to term this process "endocarditis" and, second, to believe that the vegetations develop secondary to an injury to the valve, caused by the infectious agent of rheumatic fever, which is at present unknown. Undoubtedly, fibrosis develops in the valve as a result of the inflammatory process. The inflammation is only moderate in degree and the amount of scar tissue which forms diffusely in the valve is only moderate in amount. The valve is made slightly thicker and less elastic as a result of these changes. The verrucæ become organized, then converted into fibrous tissue, and this also adds to the irregularity and loss of resiliency of the valve. Such a valve is less resistant to the strain which it must undergo in opening and shutting many times a minute and in withstanding the intracardiac pressure during the heart beat. Its lessened elasticity will cause it to open and close somewhat more slowly than normally and this will, therefore, cause slight slowing of the blood stream past the valve, and possibly, whirls or eddies in the blood stream. These two changes in the blood stream are conducive to thrombus formation. It is also conceivable that some unusual strain on the heart, and, therefore, on the somewhat compromised valve, might cause a minute injury to the valve, such as a microscopic tear in its endothelial covering. In the presence of a slowed blood stream this microscopic surface lesion would tend to add another factor toward inducing a minute thrombus, i. e., a verrucous vegetation, to form on the valve. The subsequent organization and fibrosis of this vegetation would cause further thickening and fibrosis of the valve. This would complete a vicious cycle consisting of recurring minute thrombi on the valve, very gradual thickening, with increasing susceptibility to further thrombi until a much deformed valve would result. During the process of the slow development of this valve defect, extending over many years, the valve and heart apparently might be performing their function in a satisfactory manner and no symptoms or physical signs be evident. Finally, when a seriously defective valve has developed the efficiency of the myocardium will become impaired and both symptoms and signs of chronic cardiovalvular disease will be manifested.

It is well known that recurrent attacks of acute rheumatic fever are prone to occur and often these recurrences each add marked insult to the already damaged heart valves and hasten the development of a



Fig 8—Chronic cardiovalvular disease, mitral valve Two, low, rounded projections of surface with whorllike arrangement of connective tissue of valve beneath each projection

valvular defect We must note that repeated rheumatic inflammations of the valves are undoubtedly sufficient, without any other agency, to produce even the severest grades of valvular disease It is, therefore, not necessary after repeated attacks of rheumatic fever have occurred, to hypothecate additional factors for causing the progress of sclerosis in the heart valves The surface lesions in cases of acute rheumatic endocarditis, however, present so many points of similarity to lesions on sclerosed valves, which are not rheumatic in origin, that this similarity suggested the idea of the possible significance, cause and effect of all verrucous-like, nonbacterial vegetations in the development of chronic cardiovalvular disease

It must be recalled that an appreciable number of cases of chronic cardiovalvular disease occur in adults who have a history of only a single attack of acute rheumatic fever occurring in childhood or early life These chronic valve lesions are attributed by clinicians to the previous attack of rheumatic fever The explanation has not been given of how the single trauma to the heart valves long before, causing no symptoms for many years, may finally be the cause of marked valvular defects and their consequences One attack of acute rheumatic endocarditis produces a comparatively slight valvular lesion This may give rise to no immediate symptoms or heart murmur It is evident that the valve defect, which is the final stage of the process, has developed slowly The cases under discussion give no history of subsequent attacks of acute rheumatic fever or other infectious diseases to account for the development of the severe valve lesion The explanation given here of recurring, minute verrucæ, always followed by fibrosis, would satisfactorily account for the progressive change from a slightly damaged valve to a markedly damaged one years later

Verrucæ in Chronic Nonbacterial, Nonrheumatic Cardiovalvular Disease—These lesions must have some significance, and some effect Theoretic considerations, quite similar to those already stated, might also apply here Some general toxic or some distant infectious process might result in a primary trauma to a heart valve, such as bacterial toxins from a serious pneumonia, repeated attacks of tonsillitis, the virus of scarlet fever, etc Thickening of the valve follows, and these thickened valves have been found to be free from bacteria Thus, the process of valve thickening can be regarded as nonbacterial in origin The thickened valve is more susceptible to both normal and unusual strain Microscopic lesions form, followed by verrucæ, and these in turn, by fibrosis Following this, the sequence of progressive changes may occur in the same manner as has been described as possible after a single attack of acute rheumatic fever This may eventually produce marked stenosis with a shelflike formation at the line of valve closure

Cardiovalvular Lesions in Atherosclerosis—Fibrosed, thickened and stenosed valves, found in general atherosclerosis can be explained similarly. The unusual amount of calcareous deposit in these cases is undoubtedly part of the process of atherosclerosis, probably initiating the valvular lesion and undoubtedly contributing markedly to its progression.

Aseptic Endocarditis and Chronic Cardiovalvular Disease in Congenitally Abnormal Hearts—Congenitally abnormal hearts, which at necropsy show thickening and fibrosis of their valves, usually show no inflammatory reaction in the valves. The thickening is similar to that found in chronic valvular defects in adults. This does not include those with a superimposed bacterial endocarditis.

It must be granted that abnormal openings in a heart, or stenosis of its valves, result in one or several occurrences, such as, slowing of the circulation in the heart, whirls or eddies in the circulation, direct impinging of the blood stream on abnormal endothelial sites, etc.

A heart of this type is working under a strain. This is exemplified clinically by evidence of cardiac insufficiency occurring more easily after muscular activity in persons who have congenitally abnormal hearts than in normal persons. Poor or retarded physical development in children with congenital hearts is well known, and is another evidence of the inefficient cardiac mechanism. Such a heart and its valves are undoubtedly abnormally susceptible to a strain.

One can only consider hypothetically the possible result of this susceptibility to strain and of the abnormal course of intracardiac circulation and attempt to correlate it with the findings in other similar conditions. A few data of the effect of abnormal circulation and slowing of the circulation in the more common types can be brought forward before passing on to the theoretic considerations. A number of cases are on record in which, in aortic insufficiency, valvelike structures similar to the valves in the veins, developed on the interventricular septum below the aortic valves. This is the region where the regurgitated blood passes back through the aortic ring and impinges on the septum. Also, thrombus formation, due to slowing of the circulation because of chronic cardiovalvular disease is not uncommon in the auricular appendages. These appendages, because of their location, are more likely than any other structure to accommodate a slowed circulation or eddies in the circulation. These lesions are marked evidence of the effect of abnormal intracardiac circulation and slowing of the blood stream.

It would seem, then, hypothetically, that the following is possible. Congenital cardiac anomalies may cause the valves to be under an unusual strain from time to time. Minute, endothelial breaks, cracks, or damage may result. After these changes have occurred, fibrosed

valves may develop gradually in the manner and by the mechanism already described. Even larger vegetations may occur than those found in simple chronic valve disease. The reason may be that in congenital hearts the circulation is more abnormal, slower, and conducive to the development of larger vegetations.

Terminal Verrucous Endocarditis—These lesions can be considered to give the clue to the significance of similar valve lesions found in other conditions, and described above. The verrucæ, which are terminal, are composed also of a hyaline thrombus and would seem to be induced both by slowness of the circulation, as vitality diminishes and death approaches, and, in some cases, by an increased coagulability of the blood. Death usually occurs before these thrombi can become organized.

SUMMARY

There is no satisfactory explanation as to why a slight nonbacterial damage to a heart valve during childhood gradually progresses and years later results in a severe chronic nonbacterial cardiovalvular lesion. The etiology of many of these chronic lesions is attributed by some observers to the direct action of bacteria. This is undoubtedly erroneous. They are entirely different from the lesions of bacterial endocarditis. They, however, may be caused indirectly by bacteria through the effect of toxins.

The cause of the chronic valvular lesion in a case such as the following is not at the present time explained. There is either no history of an original insult to the heart valve, or there is a history of a single insult in childhood or youth. No subsequent symptoms of cardiac disease developed, and also, no heart murmurs, or only very slight murmurs. For many years there are no symptoms or signs of a lesion of the heart valve. Then, either slight or mild cardiac symptoms are manifested, at which time a heart murmur is found, or, no heart symptoms being present, the murmur is discovered during a routine physical examination. After this there is a more rapid progression of the heart lesion and the heart symptoms.

The question which suggests itself is, why has the lesion become manifest at this time, and what has occurred to the heart valve in the interim between the original insult to the valve and the later development of the valve lesion? The following argument is presented as a possible explanation of what has occurred. There was an original insult from one or more of the following diseases: scarlet fever, measles, tonsillitis, pneumonia, etc. The best evidence indicates that the slight cardiovalvular injury which occurs during these diseases is not caused by a deposit of bacteria in or on the valve. These lesions are, therefore, nonbacterial. (The occasional case of frank pneumococcus endocarditis

and other cases of bacterial endocarditis are not being considered here) The nonbacterial process in the valve resulted in slight or mild fibrosis The change in the valve was not serious enough to impair the heart function and cause heart symptoms , it may not have been even sufficient to have caused heart murmurs This slightly damaged valve, however, did not have the resiliency, elasticity and reserve of a normal valve The ordinary work of the heart put a strain on it With the slight thickening of the valve a slight abnormality of the circulation over and around the valve occurred, which resulted in slight whirls or eddies, or slight slowing of the blood stream Activities such as heavy lifting, or exercise, may have resulted in so much strain that a microscopic damage, which would not happen normally, was inflicted on the endothelium of the valve At the site of this damage a minute thrombus was deposited The whirls in the circulation about the valve, or the slight slowing of the blood stream, helped in the formation of this thrombus This thrombus is the aseptic, verrucous, endocardial lesion or vegetation described herein This verrucous vegetation became organized, then fibrosed and incorporated in the valve, adding to its thickening and fibrosis This process still further lessened the elasticity, resiliency, etc , of the valve and rendered it more liable to subsequent minute injuries, verrucae, and the result of organization of these verrucae Thus, a vicious cycle is completed, each minute injury and its repair rendering the valve more susceptible to further injury

It is a common observation that mild degrees of thickening in the heart valve are found at necropsy, which have caused no murmurs or heart symptoms during life Therefore, it is conceivable that the progressive change in the heart valve, which has been hypothesized above, gives rise to no heart murmurs or heart symptoms until a certain stage is reached By that time quite a marked change in the valve is present This markedly changed valve is especially susceptible to injury, and after this stage occurs, further progress in the lesion is more rapid With the deformity or defect in the valve which eventually develops, the function or mechanism of the heart becomes affected and cardiac symptoms appear

The manner in which a cardiovalvular defect eventually causes sufficient disturbance in myocardial function to precipitate signs or symptoms of myocardial insufficiency is not yet completely understood Some subjects may go for years with a marked mitral stenosis and a perfectly compensated heart Some subjects with no lesions of the heart valves may die from myocardial weakness due to one of many causes, such as, coronary artery disease, so-called cardiac rheumatism, toxemia of a severe infectious disease, etc

It would seem that a valvular defect, even a serious one, if the myocardium has not also suffered damage, in many cases exists for

a long time before the interference with the cardiac function which follows causes insufficiency of the myocardium. There is great need for investigation of the manner in which chronic valvular defects cause deleterious functional and organic changes in the myocardium.

The evidence which has been presented to explain the progress of chronic, nonbacterial cardiovalvular disease is not necessarily conclusive, and it might be considered that the hypothesis has not been proven. All stages of the progress in these valve lesions are not available for study, but the similarity of the verrucous lesions in all the conditions described strongly indicates that a simple, fundamental process is the basis of all of them. This process seems to be an attempt at repair. It is evidently an imperfect attempt, such as occurs in arterial thickening in atherosclerosis. It is, therefore, another imperfect adaptation of the protective processes of nature. The repair of the heart valve results in fibrosis, lessened resistance to strain, more damage and consequent progress of the vicious cycle which has been established. In some cases even marked stenosis of the valve may result. This is an imperfect result of repair by nature, just as an aneurysm which occurs in atherosclerosis is the result of an imperfect repair. Other instances of the result of an imperfect adaptation of nature for the purpose of repair, are thrombosis in a blood vessel and its sequels, stenosis of the coronary artery in atherosclerosis, etc.

It is hoped that these hypothetic considerations, in spite of their possible incompleteness or imperfections, may direct attention to the processes described, and if the hypothesis is not justified by subsequent observation, that it may stimulate other investigations of the cause of development and progression of chronic cardiovalvular defects.

BRONCHOSPIROCHETOSIS IN CHINA¹

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PEKING, CHINA

Bronchospirochetosis was first discovered by Castellani in 1905 in patients seen in Ceylon. The spirochetes which he found to be the causative agents of the disease were described by him in 1907 under the name of *Spirochaeta bronchialis*. About the same time Bertarelli and Volpina noted spirochetes in the sputum of persons suffering from heart disease, while Rona found similar organisms in cases of pulmonary gangrene. Since then instances have been reported from many localities. Lurie¹ recorded the presence of the disease in China, although the first and only published case history I have been able to find is that of Lee² from Wusih.

In view of the widespread incidence of bronchospirochetosis in Europe, North America and in parts of Asia (Ceylon, Philippines and Siam), I have been surprised to find records of the infection almost wholly lacking for China. In collaboration with Dr C McA Wassell I started an investigation of the subject at the Church General Hospital, Wuchang, among patients suffering from hemoptysis, and discovered that the percentage of cases with bronchospirochetidial involvement was markedly high. Examination of suspected cases in other localities in China has revealed a similar condition.

Etiology and Description of the Parasite—The disease is due to infection with a spirochete known as *Spirochaeta bronchialis*. The infection has been referred to as "Castellani's bronchitis," "bronchopneumonia spirochetosis" and "bronchospirochetosis." The organism is polymorphic, with size variations of from 5 to 25 microns in length and from 0.2 to 0.3 microns in width, depending, in part, on the stage of development. Typical individuals have acuminate ends and from five to seven coils. Thus the organism as seen may be thick and short with few undulations or it may be thin and delicate with several coils. Since the short forms with few coils represent stages that have recently arisen from division of the parent organisms they are less apt to have pointed extremities than longer individuals. The organism may be viewed either in fresh smears with dark-ground illumination

* Contribution from the Parasitology Laboratory, Department of Pathology, Peking Union Medical College. Read before the Peking Branch of the China Medical Missionary Association and the Faculty Medical Club of the Peking Union Medical College, Nov 23, 1921.

1 Lurie, G. A. Notes on "Castellani's Bronchospirochetosis," with Report of a Case, *J Trop M & Hyg* **18** 269, 1915.

2 Lee, C. M. Bronchospirochetosis, with Report of Case. *China M J* **32** 332, 1918.

or in stained preparations I have found a 2 per cent aqueous solution of gentian violet well suited for such staining. In many stained organisms multiple division forms (coccoid bodies) are seen. These are believed to represent the infective stage and are thought to be transmitted by droplet spray in coughing and expectoration.

The life history of *Spirochaeta bronchiale* has been worked out definitely by Fantham³ who finds it to be a distinct species. No intermediate host is required. Moreover, Chalmers and O'Farrell⁴

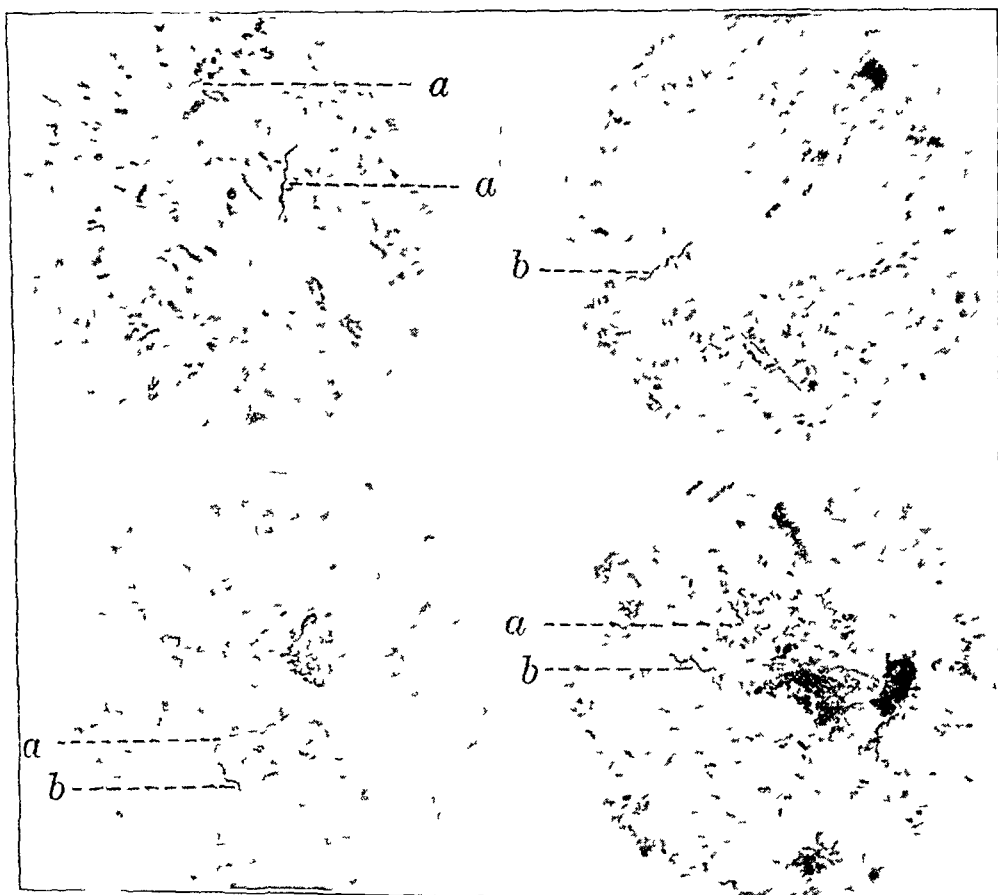


Fig 1—*a*, Vegetative organisms *b*, Division forms. Note clear spaces between chromatin areas. $\times 720$

have shown by experimental infection of man and monkeys that this is the actual causal agent of bronchospirochetosis.

The diagnosis is made by examining the sputum in a suspected case and finding the organism, *S. bronchiale*, which may be differentiated

³ Fantham, H. G. *Spirochaeta Bronchialis*, Cast 1907, together with Remarks on the Spirochaetae of the Human Mouth. *Ann Trop Med & Parasitol* 9:391, 1915.

⁴ Chalmers, A. J. and O'Farrell, W. R. Bronchial Spirochetosis, *J Trop M & Hyg* 16:329, 1913.

from the buccal spirochetes by ascertaining (1) that it comes from the exudate of the trachea or bronchi, and (2) that it is not associated with the fusiform bacilli of Vincent's angina. Thus far, aside from size, actual morphologic differences from the mouth spirochetes have been difficult to demonstrate.

The disease may be simple or it may be complicated with pneumonia, pulmonary gangrene, empyema, tuberculosis of the lungs, moniliasis, paragonimiasis or rhinitic spirochetosis. While a certain proportion of cases in China will be found to be free from complications, a large share of them will probably prove to be primarily cases of pulmonary tuberculosis with a complication of bronchospirochetosis. In either instance it is extremely important to examine for these spirochetes the sputum of all persons giving a history of hemoptysis. If the spirochetes is found to be the primary agent of the disease, relief is easily effected. If the disease is complicated by some other infection, then spirochetosis can be eliminated, leaving the physician free to treat the primary agent of the disease.

Bronchospirochetosis may manifest itself as an acute attack or it may be chronic or subacute in its nature. In acute cases a chill develops, then fever, which, according to Castellani, seldom exceeds 39.5 C. This lasts for from two to eight days, during which time the patient coughs almost continuously and complains of pains all over the body. The expectoration is scanty, mucopurulent, very seldom containing traces of blood. This type is not likely to be found often in clinics in China, since the patient is reluctant to consult the physician until Chinese medications have been found ineffective. While arsenicals produce rapid relief, the clinical symptoms may disappear even without treatment.

In the subacute type the general symptoms are similar to those of the acute type, but there may be hemoptysis and bronchitis, with slight crepitations.

In the chronic type the disease may have been slow and insidious in onset, or the patient may give a history of previous acute attacks. When he comes for treatment he has a chronic cough, the sputum is mucopurulent, often bloodstreaked, while in many instances there is considerable hemoptysis. There may be moist or dry râles or consolidation areas.

In many cases there is a daily rise of temperature, sometimes reaching as high as 40.5 C. This is the usual type of patient to be dealt with in China, who will present himself at the tuberculosis clinic. In most instances rest and treatment with liquor potassii arsenitis (Fowler's solution), cacodylates, arsphenamin, or neo-arsphenamin, will bring about rapid recovery and apparent cure.

Cases of lung gangrene, empyema, fetid bronchitis and rhinitis are on record, in which *Spironema bronchiale* or a similar organism has been the only pathogenic body isolated, but such instances are rare compared with the usual chronic type

Preliminary inquiries have revealed the presence of bronchospirochetosis in the following centers in China Amoy, Nanking, Wusih, Wuchang, Pao Ting Fu and Peking

Through the kindness of Dr J P Maxwell I can report three cases of simple bronchospirochetosis from Amoy, Fukien Province, with no microscopic evidence of tuberculosis Two of the patients were Northern soldiers, while one was a native of Fukien Province They were probably all of the chronic type, with a variable amount of sputum, often streaked with blood Treatment with tonics and potassium iodid was helpful "as far as immediate results were concerned"

Out of five cases found positive for tubercle bacilli in the sputum in the Nanking Hospital in September, 1921, four were also positive for *Spironema bronchiale* These were all chronic cases Dr Hutcheson has recently found several cases of simple bronchospirochetosis

Lee's record² for Wusih was that of a chronic case, with a history of hemoptysis Repeated examinations for tubercle bacilli were unsuccessful Sodium cacodylate per orem brought about rapid recovery

In September, 1921, Dr J H Wylie of Paotingfu brought me smears of sputum which contained *Spironema bronchiale* in large numbers Several examinations by Dr Wylie revealed no tubercle bacilli On entering the hospital, the patient had marked hemoptysis, which recurred every three or five days He was quite anemic He remained in the hospital about three weeks, during which time he was given three intravenous injections of neo-arsphenamin, the first consisting of 0.45 gm and the second and third of 0.6 gm each After the third dose his sputum was free from spirochetes Other cases have more recently come to Dr Wylie's attention, including one with a history of syphilis and one in which death resulted from pulmonary tuberculosis

I have more recently been able to confirm the presence of the parasite in patients in Peking giving similar clinical histories

Through the kindness of Dr C McA Wassell I have had an opportunity to study several cases of bronchospirochetosis from the Church General Hospital, Wuchang Five of these cases have been available for analysis and are briefly presented here

REPORT OF CASES

CASE 1—Chronic Type (Chart 1)

History—Chinese soldier, aged 25, complained of profuse expectoration, about 300 cc per day, blood streaked, loss of weight, painful cough and fever

Family history—negative One friend died of hemoptysis recently At 11 years of age he had profuse nose bleeding At 20 he had tertian malaria At

21 he had gonorrhea June, 1920, he had blood-tinged expectoration and was treated by a native doctor He has not been well since He has had recurrent attacks with fever, expectoration, but no night sweats Two months previously he suffered exposure on a long march, resulting in coryza and profuse expectoration This condition prevailed up to the time of his examination

Physical Examination—On admission to the hospital the patient's temperature was 38.5 C, pulse 76 and respirations 20 He was physically weak, hollow eyed, with cold perspiration all over the body His mind was clear, eyes reacted normally, and skin was of a good color Nose, lips, palate and pharynx were slightly congested The teeth showed some caries as well as pyrrhea Neck glands were slightly enlarged in left submaxillary region but without fluctuation Larynx was without tracheal tugging Chest was without deformation and with normal respiration On percussion a dulness was demonstrated in the right axilla above the liver and in the right scapular area The right lung above scapula showed coarse crackling râles, which were quite audible on soft coughing Fine moist râles were found in the right midaxillary line between the eighth and ninth ribs The bones and extremities were normal Reflexes, normal

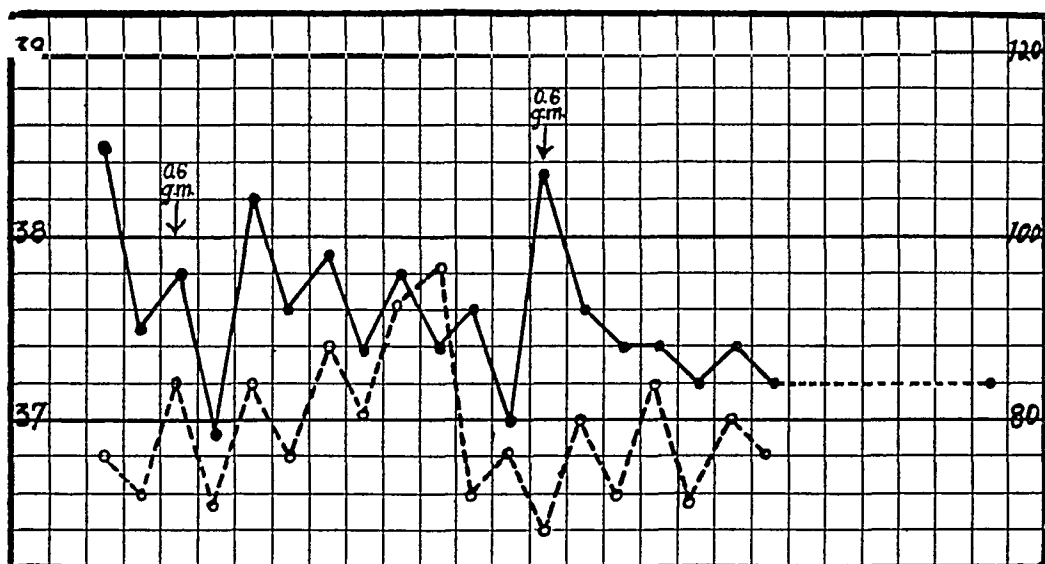


Chart 1—Wuchang Case 1 Simple chronic bronchospirochetosis

Laboratory Data—The sputum was negative for tubercle bacilli after repeated examinations, but was positive for spirochetes after rinsing of the mouth The feces were positive for ascaris, ancylostoma and cysts of *Endameba dysenteriae* and *E coli* The urine gave an acid reaction, was orange in color and had a specific gravity of 1.030 On entrance the blood was positive for *Plasmodium vivax*, showed a red count of 4,450,000 and a white count of 12,700, with 75 per cent hemoglobin Eosinophils were 12 per cent A tentative diagnosis of bronchospirochetosis and tertian malaria was made

Clinical Data—On the day after admission, the patient was treated intravenously with 0.6 gm of neo-arsphenamin The temperature remained between 37.5 and 38.2 C for five days, although there was a general note of improvement On the seventh day the temperature rose to 38.5 C, whereupon a second administration of neo-arsphenamin was made (0.6 gm) The temperature then returned to normal and remained so until the patient was discharged Blood examination on the fifth day showed a slight increase in reds (4,864,000) and a decrease in whites (9,100), with a marked reduction in eosinophils (6.3 per cent) The reds increased to 6,000,000 on successive examinations, while the white count was reduced to 7,000 The eosinophils remained high until clinical symptoms disappeared On the eighth and successive days the spirochetes were

not found in the sputum. At the same time the lungs became clear, the râles and dulness disappeared and the general condition of the patient was markedly improved. He was discharged on the ninth day and three months later showed no recurrence.

CASE 2—Chronic Type (Chart 2)

History—Chinese farmer, aged 18, complained of dyspnea, cough, expectoration and at times hemoptysis, also ulcers of feet due to wearing grass shoes. Family history negative. No disease of childhood, except chronic profuse expectoration since 9 years of age, with hemoptysis at 12 years.

Physical Examination—On admission to the hospital, the patient's temperature was 37.4 C, pulse 100, respirations 24. He was of ordinary build and fairly well nourished. Intelligence good, speech alert. Skin good, intact except for ulcers on feet. Membranes of both nares red, inflamed. Lips inflamed and feverish. Pharynx without exudate, tonsils normal. Teeth and gums good. Palate normal, no laryngeal tugging. Glands in neck enlarged on both sides along sternocleidomastoid muscles. Thyroid somewhat enlarged, no pulsations. Chest full, normal. Dyspnea. Right axillary space dull to percussion. Breath sounds over right axillary space hard and tubular. Few fine râles under right nipple and over right base along spinal border. Extremities normal except for ulcers on feet.

Laboratory Data—Sputum negative for tubercle bacilli after repeated examination, but positive for spirochetes. Feces positive for ascaris. Urine, a light straw color, acid in reaction, with a specific gravity of 1.005, positive for traces of sugar. On entrance, the blood was negative for malaria, with a red count of 4,000,000 and white count of 8,700. Eosinophils numbered 18 per cent. An admission diagnosis of bronchospirochetosis and ulcer of the foot was made.

Clinical Data—Soon after admission the patient's temperature rose to 38.1 C, then dropped to 36.8 C. On the tenth day, 0.45 gm neo-arsphenamin was administered intravenously. The temperature was reduced and remained near normal until discharge, twenty-six days after entrance. Spirochetes disappeared from the sputum two days after administration of the arsenical and did not reappear. Meanwhile the blood picture improved (red count 4,700,000, white count 6,800) although the eosinophilia remained pronounced (from 16 to 17.5 per cent). The patient was discharged as improved.

CASE 3—Chronic Type

History—Chinese soldier, aged 25, complained of weakness, profuse expectoration, bad cough, hemoptysis. Family history negative. Patient had no illness up to the age of 24 years, at which time he had hemorrhages, cough and weakness. This continued intermittently, becoming more pronounced after extra exertion.

Physical Examination—On admission to the hospital the patient's temperature was 36.0 C, pulse 90 and respirations 20. His general appearance was normal. Skin negative. Nose slightly inflamed in left turbinal area. Lips, teeth, palate, neck and larynx all negative. Chest with moist bubbling râles along both borders of sternum and at left apex. Extremities and bones negative.

Laboratory Data—The sputum was negative for tubercle bacilli on successive examinations but was positive for spirochetes. The feces were positive for trichuris. Urine was negative. On admission the red cells numbered 6,100,000 and the white cells 5,000. Eosinophils were 20 per cent. A tentative diagnosis of bronchospirochetosis was made.

On the day after admission when a rise in temperature was observed, the patient was treated with 0.45 gm neo-arsphenamin. This caused improvement so that on the fourth day the sputum became negative for spirochetes, and the eosinophilia was reduced one-half. The general improvement of the patient was soon observed. He left the hospital on the sixth day, but returned two days later for a second administration of 0.45 gm neo-arsphenamin. He was apparently helped.

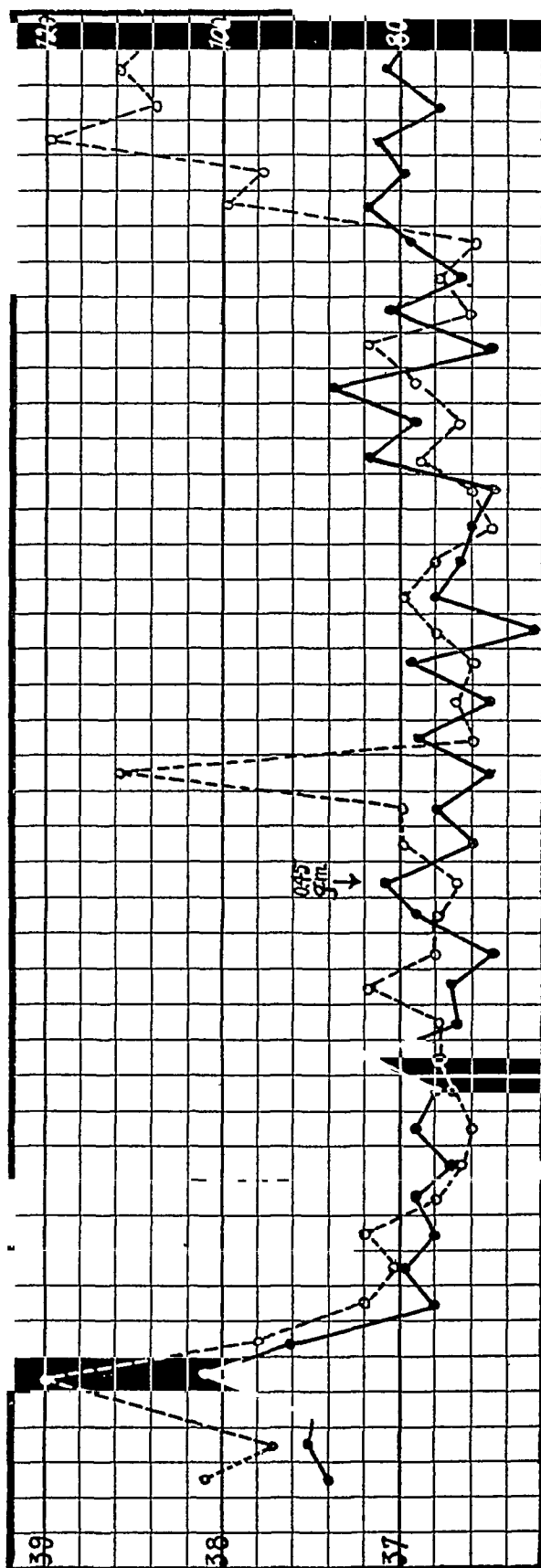


Chart 2—Wuchang Case 2 Simple chronic bronchospirochetosis and ulcerated foot

CASE 4 — Pulmonary tuberculosis complicated by bronchospirochetosis (Chart 3)

History—Chinese soldier, aged 24, complained of expectoration and dyspnea. Family history negative. Past history with record of smallpox, malaria and gonorrhea. Two months previously patient noted pinkish sputum and felt ill. He had night sweats and afternoon fever. He became weaker day by day with increased dyspnea. Stool was fluid since attack.

Physical Examination—On admission the patient's temperature was 37.8 C, his pulse 126, and his respiration 26. Nutrition poor, malaise. Anemia pro-

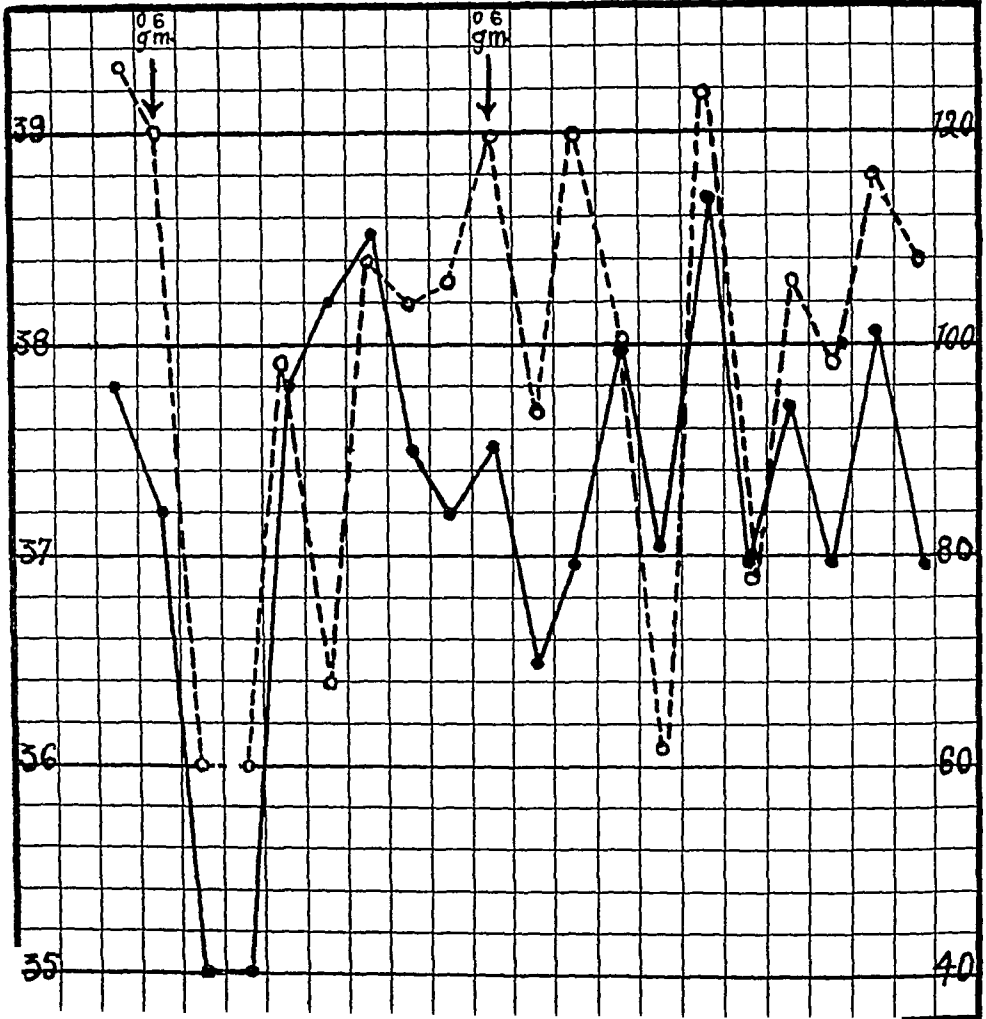


Chart 3—Wuchang Case 4 Pulmonary tuberculosis complicated by bronchospirochetosis

nounced in eyes, lips, skin and gums. Neck glands hard, no enlargement or pulsation. Tactile fremitus decreased in right axilla. Dulness over a triangular area under right axilla and behind this area. Moist râles above and between these areas. Extremities and bones negative. Reflexes normal.

Laboratory Data—The sputum was positive for tubercle bacilli and for spirochetes. Feces were positive for ascaris and for *Endameba coli* cysts. Urine was yellow, acid in reaction, of a specific gravity of 1.010, with a slight trace of sugar. The red count was 4,400,000 on admission while the white count was 10,500. Eosinophils were less than 1 per cent. A tentative diagnosis of pulmonary tuberculosis and of bronchospirochetosis was made.

Clinical Data—Two days after admission, 0.6 gm neo-arsphenamin was administered intravenously. This was followed by profuse sweating and a chill, with a reduction of temperature to 35.0 C. After two days it mounted to 37.8 C. On the sixth day, a second administration of 0.6 gm neo-arsphenamin was given, which was followed by a chill. Temperature remained irregular up to the time the case left the hospital. The sputum was negative for spirochetes after the fifth day but remained positive for tubercle bacilli. The red cells rose to 5,745,000 and the white cells were reduced to 6,700 after one week's time, but the general condition of the patient did not improve.

CASE 5—Pulmonary tuberculosis complicated by bronchospirochetosis

History—Chinese cloth-weaver, aged 29, complained of cough, tightness in chest, dizziness, borborygmus, fever and pain in right breast. One sister and an intimate friend gave histories of hemoptysis. Diseases of childhood were confined to malaria and epistaxis. A year ago the patient had coma and numbness of the extremities, followed by dyspnea and dizziness about once a month. Patient denied having night sweats or afternoon fever or any exposure. Three months ago he had chills and fever followed by cough and sore throat. A white mucoid expectoration developed and a month later blood was found in the sputum. This continued intermittently until he entered the hospital.

Physical Examination—On admission the patient's temperature was 38.4 C, his pulse 88, and his respirations 20. He had a well developed body, was well nourished, although slight anemia was evident. The lips were dry and feverish. Gums showed anemia. Tonsils, palate and pharynx were negative. No enlarged neck glands. Dulness in right lung near scapula. Rales were noted both on expiration and inspiration. Extremities were normal. Reflexes, normal.

Laboratory Data—The sputum was positive for spirochetes on admission and was later found to contain tubercle bacilli. The feces were positive for ascaris. The urine was yellow, gave an acid reaction, had a specific gravity of 1.018 and showed a slight trace of sugar. The red cell count was 4,000,000 and the white cell count was 12,000. Eosinophils were less than 1 per cent. A tentative diagnosis of pulmonary tuberculosis and bronchospirochetosis was made.

Clinical Data—The day after admission, the patient was given 0.6 gm neo-arsphenamin, which was followed by a chill and profuse sweating. For the next three days the temperature ranged from 37 to 38 C. On the sixth day a second administration of 0.6 gm neo-arsphenamin was given, which was without marked reaction. The spirochetes disappeared from the sputum two days after the first injection of neo-arsphenamin. The blood picture on the sixth day showed 5,400,000 red cells and 6,900 white cells with no increase in eosinophils. On the eleventh day the temperature and other symptoms showed such improvement that the patient asked to be dismissed.

DISCUSSION

A survey of the Chinese cases of bronchospirochetosis indicates two things. In the first place, a certain proportion of the subjects have pulmonary tuberculosis as a primary infection with a secondary spirochetosis. Secondly, cases of simple bronchospirochetosis are usually of the chronic type, giving a history of recurrent cough and hemoptysis for a period of from one to ten years. They differ markedly, then, from Chalmers and O'Farrell's experimental case⁴ and from the cases cited by Bloedorn and Houghton.⁵ In Chalmer's case the infection was under observation from the day of its inception. In each of

⁵ Bloedorn, W. A., and Houghton, J. E. Bronchial Spirochetosis, J. A. M. A. **76** 1559 (June 4) 1921.

Bloedorn and Houghton's cases only a few days elapsed from the time the patient noticed the acute attack until he came to the hospital for treatment. In simple acute cases the picture is uncomplicated by other activating agents of disease. The observations are easily made and the symptoms are readily attributed to the single infective agent. These cases are also easily studied from the temperature graph.

Chinese cases are not so readily reduced to simple formulas. Granted that acute attacks of bronchospirochetosis are not uncommon among the Chinese, the fact that the patient in many communities comes to the hospital as a last resort means that the case has run a considerable course and has probably recurred several times before the physician has an opportunity to observe and treat it. The temperature in such chronic cases is lower and less regular than in acute cases. When the primary infection is pulmonary tuberculosis, both temperature and pulse are erratic and remain irregular after the spirochetes disappear from the sputum. In other words, relief from the spirochetosis does not appreciably simplify the picture.

In acute bronchospirochetosis, arsenicals, injected intravenously, give immediate relief. The fever drops, the pulse becomes regular and the respiration normal. This important improvement is obtained from the initial dose but ordinarily a second and, perhaps, a third administration are necessary for recovery. Bloedorn and Houghton used 0.6 gm neo-arsphenamin as an initial dosage, followed by 0.5 gm (?), and then by 0.9 gm, repeated at weekly intervals. The first three injections were apparently necessary for recovery, although immediate administration of the arsenical on admission to the hospital, instead of two weeks later, might have reduced the amount of treatment necessary. In the Chinese cases, in spite of the chronic nature of the infection, arsenicals are specific and relatively rapid in their spirocheticidal properties. Wylie gave an initial dose of 0.45 gm and a second and third dose of 0.6 gm, each. A similar result was obtained for Wuchang Case 1, although the amount of neo-arsphenamin was slightly larger. The temperature drops almost immediately after each injection and is not followed by chills and sweats as when complicated by pulmonary tuberculosis. It remains nearly normal after the second dose, although the spirochetes do not usually disappear until some time later. Furthermore, there is usually a marked general improvement. The effect of this spirocheticide on the disease, even in an aggravated chronic stage, apparently meets Manson-Bahr's objection⁶ that the causal relationship of *Spironema bronchiale* to the bronchial infection in which it is found has not been proved.

⁶ Manson-Bahr, P. H. *Manson's Tropical Diseases, a Manual of the Diseases of Warm Climates*, London, Cassell and Co., 1921, 960 pp.

In tuberculous infections (Wuchang, Cases 4 and 5) the administration of arsenicals eliminated spirochetes from the sputum but did not materially relieve the patient. Temperature and irregular pulse persisted, while no bodily improvement was noted.

The administration of potassium iodid, sodium cacodylate and other therapeutic agents has been found valuable in bronchospirochetosis, but per os treatments do not have such specific properties as does the intravenous administration of arsenicals. Single doses of the latter alleviate, but, apparently, a cumulative effect is required for killing the spirochete.

A most interesting phase of the study of bronchospirochetosis is the blood picture. In all cases on record there is a reduction in red cells and a reduced hemoglobin percentage. The leukocytes may be either reduced, increased or normal. In one of Chalmers and O'Farrell's cases, an Arab, the red cells numbered 3,648,000 per c mm during the attack and 4,400,000 per c mm during the interval between attacks, with 80 per cent hemoglobin during the attack and 100 per cent in the interval. There was a marked leukopenia, 2,719 per c mm, with eosinophils 2.6 per cent of the total.

Nolf's case 2,⁷ the only one of his histories with a complete leukocyte picture, showed a slight leukopenia (from 4,400 to 4,800), with 1 per cent eosinophils.

The Chinese cases reviewed vary as to the red count, but all show a reduction in the number of cells and in the percentage of hemoglobin. One case shows a leukopenia (5,000), one case is only slightly above normal, while three cases show a leukocytosis. In each case the picture approaches normal with treatment. Of greater interest, however, is the grouping on the basis of the eosinophils. With tuberculous complication the eosinophil count, as observed, is less than 1 per cent. In the other three cases (simple infection) eosinophilia is extremely high (from 12 to 20 per cent). This high percentage is reduced after treatment. It seems worth while, therefore, to inquire into the possible value of the eosinophil index as a means of ascertaining whether bronchospirochetosis, as determined by detection of the spirochete in the sputum, is a simple infection or constitutes part of a more complicated picture.

If one regards all varieties of spirochetes of the respiratory tract (exclusive of the mouth) as *Spironema bronchiale*, but capable of different manifestations, the organism must, then, be considered as highly adaptive. However, Nolf's organism⁷ differs considerably from the typical agent of bronchospirochetosis both in structure and in the effect on the host. It seems probable, therefore, that it belongs to a

7 Nolf, P. Fetid Spirillar Bronchitis and Pulmonary Gangrene, Arch. Int. Med. 25:429 (April) 1920.

different group. There yet remain those types causing rhinitis, those with bronchial and lobar involvement and those with only bronchial infection. There is also the record of bronchial spirochetosis with pleural involvement (Mason⁸). It seems possible that careful examination will reveal all of these several types in China.

In cases that have been called to my attention, the spirochetes are more readily demonstrated in subacute cases than in chronic ones. Furthermore, there is some evidence to support the view that they can be recovered more easily from mucopurulent sputum several hours after an attack of hemoptysis than in the blood streaked sputum.

While the records from China cited here are incomplete and show the need of further observation, it is hoped that these preliminary data will serve as a stimulus to observation of the disease in other centers in China, and to more thorough study of both the clinical and laboratory evidence of the infection. Such study is especially important in view of the widespread incidence of pulmonary tuberculosis in China. Detection and treatment of simple infection with bronchial spirochetes will not only bring immediate relief to such cases but will reduce the amount of routine observation and diagnosis in suspected tuberculosis patients who do not react to tuberculin.

⁸ Mason, V. R. Pleural Spirochetosis, *Johns Hopkins Hosp. Bull.* **31** 435, 1920.

TETANY

A REPORT OF CASES WITH ACID-BASE DISTURBANCE *

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The symptoms of tetany occur in a number of widely differing conditions, such as disease of the stomach, overdosage with sodium bicarbonate, prolonged hyperpnea, absence of the parathyroid glands, and in infants as a clinical entity often associated with rickets. Recently there has been a considerable amount of research into the physiologic phenomena underlying the increased irritability of nervous and muscular tissues in these conditions, and various theories as to its etiology have been advanced. The chief of these are that it is due to a disturbance of the acid-base equilibrium in the body and to a disturbance of the calcium metabolism.¹

Acid-base disturbance, consisting of an increase in the ratio of sodium bicarbonate to carbonic acid, is found in overdosage with sodium bicarbonate, in prolonged hyperpnea and in pyloric obstruction. The uniform hydrogen ion concentration of the body fluids is largely dependent on the maintenance of a constant $\frac{\text{Na H CO}_3}{\text{H}_2\text{CO}_3}$ ratio, according to the generally accepted view, and any marked increase in the ratio might be expected to result in a shifting of salt balance, and physiological disturbances in the body.

In overdosage with sodium bicarbonate (NaHCO_3) this agent is added to the blood faster than it is neutralized or excreted, hence the "alkali reserve" becomes greatly increased,² and there is presumably an increase in the ratio. In hyperpnea the carbonic acid in the blood is decreased by washing out of carbon dioxide faster than sodium bicarbonate is decreased by excretion or neutralization, and there is thus a relative excess of alkali, and an increase in the ratio.³ In tetany with pyloric obstruction the explanation is held to be quite different. Hydrochloric acid, formed by the reaction $\text{NaCl} + \text{H}_2\text{CO}_3 = \text{HCl} + \text{NaHCO}_3$, is secreted into the stomach, but in the presence of pyloric obstruction cannot pass through to the intestines to stimulate the alkaline intestinal secretion. There is, therefore, left in the blood

* From the Medical Clinic of the Peter Bent Brigham Hospital

1 Wilson, Stearns and Thurlow. *J Biol Chem* **23** 89, 1915. Wilson, Stearns and Janney. *J Biol Chem* **23** 123, 1915. McCann. *J Biol Chem* **35** 553, 1918. MacCallum and Voegtlin. *J Exper M* **11** 118, 1909. MacCallum and Vogel. *J Exper M* **18** 618, 1913. Howland and Marriott. *Quart J M* **2** 289, 1918. Kramer, Tisdall and Howland. *Am J Dis Child* **22** 431 (Nov) 1921.

2 Harrop. *Bull Johns Hopkins Hosp* **30** 62, 1919.

3 Grant and Goldman. *Am J Physiol* **52** 209, 1920.

an excess of sodium bicarbonate This view is supported by the work of McCann,¹ who reported an increase in the plasma carbon dioxide capacity of animals in experimental tetany accompanying pyloric obstruction MacCallum and his co-workers⁴ have added the observation that blood chlorids are reduced, and Hastings, Murray and Murray⁵ have found the blood sodium content also decreased It seems not unlikely that the chlorid content is reduced by the secretion of hydrochloric acid into the stomach and loss by vomiting, and possibly sodium is decreased by excretion in an alkaline urine

Calcium deficiency in the blood has repeatedly been found in parathyroid tetany⁶ and in infantile tetany (Howland and Marriott,¹ Kramer, Tisdall and Howland¹) The majority of investigations indicate that there is no "alkalosis" in these conditions MacCallum⁴ Tokujii and Togawa⁷ and Hastings and Murray⁵ were unable to find the increase of plasma carbon dioxide reported by McCann¹ in parathyroidectomized dogs Wilson and his co-workers¹ concluded, from studies of the dissociation constant of hemoglobin, the alveolar carbon dioxide pressure, the hydrogen ion concentration of blood and urine, the ammonia content and total acidity of urine, that there is an "alkalosis" in parathyroid tetany Greenwald⁸ has recently advanced objections to the conclusions drawn from this work

Noel Paton, Findlay and Watson⁹ have found an increase in guanidin and methyl guanidin in the blood and urine in parathyroid and infantile tetany They corroborate the observation of other investigators that administration of guanidin and methyl guanidin results in hyperexcitability very similar to that seen in tetany

In a recent paper Freudenberg and Gyorgy¹⁰ have attempted to correlate all forms of tetany as being due, in the final analysis, to calcium deficiency in the tissues It is well recognized that such a deficiency leads to hyperexcitability in irritable tissues Their theory is based, among other things, on the observations that calcium union with colloids may be influenced by changes in hydrogen ion concentration, by changes in calcium ion concentration, and by such substances as phosphate, acetate, nitrate and bicarbonate ions, and by protein derivatives with free amido groups, such as methyl and trimethylamin, guanidin, methyl guanidin, creatin, etc They state, that in conditions in which there is an increase in the ratio of sodium bicarbonate to carbonic acid, free calcium ions in the blood decrease, being added to

4 MacCallum, et al Bull Johns Hopkins Hosp **31** 1, 1920

5 Hastings, Murray and Murray J Biol Chem **46** 223, 1921

6 Hastings and Murray J Biol Chem **46** 233, 1921

7 Tokujii and Togawa J Lab & Clin M **5** 299, 1919

8 Greenwald Proc Soc Exper Biol & M **18** 228, 1921

9 Paton, Findlay and Watson Quart J Exper Physiol **10** 203, 1916

10 Freudenberg and Gyorgy Jahrb f Kinderh **96** 5, 1921

the total of calcium bound with colloids in the blood. As a result of this, the equilibrium between ionized blood calcium and calcium bound with tissue colloids is disturbed, calcium enters the blood stream from the tissues, and increased irritability occurs. The calcium content in the blood should, therefore, be increased, and, as a matter of fact, very slight increases in serum calcium have been reported in tetany of hyperpnea³ and in tetany with experimental pyloric obstruction⁵. The occurrence of tetany without this acid-base disturbance they explain by the action of the protein derivative substances with free amido groups. These directly restrict calcium union with colloids, thus decreasing tissue calcium, and causing increased irritability. Calcium enters the blood from the tissues, causing presumably an increased blood calcium content at the outset. But by calcium excretion the equilibrium between blood and tissue is reestablished, blood calcium being adjusted to the lower level of tissue calcium. In this process the percentage of diffusible calcium in the blood should not be altered, and Meysenbug and McCann¹¹ have found the same percentage of diffusible calcium in normal blood and in the calcium poor blood of dogs with parathyroid tetany.

This theory of Freudenberg and Gyorgy,¹⁰ although very interesting, is by no means proved, and is not without objections. For instance, the carbon dioxide tension of serum was varied from 17 to 62 mm by Meysenbug and his co-workers¹² without any detectable change in the percentage of diffusible calcium.

Luckhardt and Rosenblom¹³ found that tetany could be prevented in parathyroidectomized dogs by injecting Ringer's solution intravenously two or three times daily. This procedure causes a marked diuresis, and presumably the elimination from the body of toxic substances such as guanidin. When the injections were stopped, symptoms of tetany developed. Of particular interest is the observation of these investigators that calcium free Ringer's solution produced the same effect as ordinary Ringer's solution, tetany being prevented when it was injected, occurring when the injections were stopped, and ceasing when they were started again. Thus, as the authors state, the production of diuresis is apparently more important than the administration of calcium in preventing tetany. However, it cannot be concluded from the fact that calcium free Ringer's solution prevented tetany, that there is no disturbance of calcium balance in this condition. Any procedure causing marked diuresis would probably have the same effect.

11 Meysenbug and McCann. *J Biol Chem* **47** 541, 1921.

12 Meysenbug, Pappenheimer, Zucker and Murray. *J Biol Chem* **47** 529, 1921.

13 Luckhardt and Rosenblom. *Proc Soc Exper Biol & M* **19** 129 1921.

Six cases of tetany in adults, in which various interesting points are illustrated, have been studied at the Peter Bent Brigham Hospital. Four of these were observed by me, and two were taken from the case histories in the hospital records.

REPORT OF CASES

CASE 1—History—J. E. W. (Med No 17581), a clerk, aged 20, entered the hospital Jan 13, 1922, with a history of intermittent epigastric distress, heartburn, gaseous eructation, nausea and vomiting extending over a period of two years. For three weeks prior to admission he had had severe stabbing and cramping pains in the epigastrium, copious vomiting and spasms of the hands and feet, the latter occurring almost daily for about a week. Because of these spasms there had been difficulty in handling small objects.

Examination—The Roentgen ray showed a greatly dilated stomach and almost complete pyloric obstruction. Fractional gastric analysis disclosed marked hyperacidity, free hydrochloric acid in 10 c.c. of the fasting contents, and in three specimens removed at forty minute intervals after the test meal, titrating with 6.8, 8.5, 13 and 8 c.c. of decinormal sodium hydroxid, respectively.

ACID-BASE EQUILIBRIUM IN CASE 1

	Plasma CO ₂ Capacity in Vol %	Plasma Chlorid * Mg NaCl per 100 C c	Whole Blood Chlorid Mg NaCl per 100 C c	Serum Calcium † Mg per 100 C c
January 18	93			
January 19	86			
January 20	87	524	250	12.4
January 21	83			
January 23	69			
January 25	72			
January 26	63	600		14
January 31	59	571	480	
February 13	69	600	436	12.5

* Method of Folin and Whitehorn

† Method of Kramer and Tisdall

Course—With rest in bed and atropin, 0.0005 gm. by mouth, three times a day, and the same dose hypodermically on five occasions during attacks of pain, the vomiting rapidly decreased, and in a few days the pains occurred only once in twenty-four hours. On two occasions there were transient spasms of the hands, but unfortunately these occurred at about 2 a. m., and were not observed. There was a definite Chvostek sign of tetany, i. e., tapping the face over the seventh nerve caused a contraction of the muscles of the upper lip. Compressing the arm above the elbow resulted in tingling and numbness in the hands, and the fingers involuntarily became partially flexed, but no definite spasm occurred. On reference to the accompanying table it is seen that January 18 the plasma carbon dioxide capacity was found to be greatly elevated. January 20, the plasma chlorids, and especially the whole blood chlorids, were reduced, the latter to 50 per cent of normal. After January 20 the epigastric pain and cramps ceased, and the patient did not vomit, except once January 22 and again January 25. The plasma carbon dioxide capacity and the plasma chlorids became normal by January 26. On this day, after the blood analysis had been done, a large duodenal ulcer was found at operation, and a gastro-enterostomy was performed. Convalescence was uneventful, and symptoms of tetany did not recur. The serum calcium content throughout was within the upper limits of normal. The fact that the whole blood chlorid was so markedly decreased, compared with the relatively small decrease of plasma chlorid, indicates that the blood cells must have been virtually free of chlorin.

CASE 2—History—G B B (Med No 14040), a foundryman, aged 43, with a history of abdominal pain and frequent vomiting for thirteen years, and occasional attacks of “cramps” in the arms and legs for five years, entered the hospital July 22, 1920, with well developed signs of tetany. The forearms, hands and fingers were in continuous flexion.

Examination—The roentgen ray showed a dilated stomach and almost complete pyloric obstruction. The plasma carbon dioxide capacity was 87.8 volume per cent.

Course—Sodium chlorid was given per rectum, intravenously and by mouth, coincident with some improvement in the patient's condition, but without evidence of the causal relationship of this therapy to the improvement, the patient having recovered from his previous attacks spontaneously. The excretion of chlorid in the urine was greatly below normal, analysis of twenty-four hour urine specimens of the second to the fifth day in the hospital showing 0.50, 1.5, 0.81, and 1.8 gm, respectively. This may be accounted for, in part, by the small amount of food which the patient was retaining. Unfortunately, the chlorid content of the blood was not determined. The plasma carbon dioxide capacity remained greatly elevated. July 23, 24, 26, 27, 30 and August 2 it was 98, 96, 84, 77, 79 and 75.5 volume per cent, respectively. The patient's general condition improved, and the spasm relaxed, but did not disappear completely. Permission to operate for relief of pyloric obstruction was refused, and the patient was discharged against advice August 3, still having occasional attacks of vomiting, and spasm of the hands when at rest. One year later it was learned that the patient was dead.

CASE 3—History—J W (Med No 6164), a stage hand, aged 55, entered the hospital Feb 19, 1917, with a history of epigastric distress and vomiting for three months, and rapid loss of weight. The day before death, after three days of very frequent vomiting, he was found to have typical spasms of tetany in the hands and forearms. One hour and fifteen minutes before death there was a “sort of convulsion,” the patient stopped breathing for a short while, and then breathed irregularly until death.

Necropsy disclosed an annular constricting carcinoma at the junction of the duodenum and jejunum. The stomach, pylorus and duodenum were greatly dilated. Liver, gallbladder and bile ducts were normal. Unfortunately, no blood analysis was done on this patient. However, the case is interesting, inasmuch as the obstruction was at the end of the duodenum, allowing the secretion of the alkaline bile and pancreatic fluids to be stimulated by the gastric contents. Fractional gastric analysis had shown a normal amount of free and combined acid in the stomach contents. Apparently the secretion of acid was relatively greater than that of alkali.

CASE 4—History—F L (Med No 14833), a female clerk, aged 23, was admitted to the hospital Nov 23, 1920, with gastric symptoms of three years' duration.

Examination—The roentgen ray confirmed the diagnosis of gastric ulcer, and treatment by the Sippy method was started.

Course—Because free acid persisted in portions of the gastric contents removed during the night, administration of alkali was rapidly increased, until the patient was receiving 10 gm sodium bicarbonate every hour, and 1.2 gm magnesium oxid and 3 gm calcium carbonate at alternate hours from 7.30 a m to 7.30 p m. At the end of the fifth day of this medication she felt nauseated, vomited once, for the first time during treatment, and noticed a prickling sensation in the hands, and “stiffness” in the face. The mouth became somewhat puckered up, so that there was difficulty in speaking, and the eyelids were partially closed. Spasm developed in the hands, the fingers becoming partially flexed, and the patient was unable to open them to hold a drinking glass. This persisted for only a few minutes, and in about ten minutes the patient felt entirely normal. Administration of alkali was discontinued, and no further spontaneous spasm occurred. The following morning the plasma carbon dioxide capacity was 90.5 volume per cent. At this time there was a definite Trousseau sign of tetany, i e, compressing the arm above the elbow resulted in

tingling and prickling sensations in the hand, gradual flexion of the fingers at the metacarpal phalangeal joints and adduction of thumb. The patient could not voluntarily overcome this spasm. There was also a faint Chvostek sign, tapping over the facial nerve caused slight twitching of the muscles about the mouth. These signs decreased somewhat, and Sippy treatment, with smaller doses of alkali, was again instituted. Three days after the appearance of tetany there were still signs of latent tetany, and the plasma carbon dioxide capacity was 91 volume per cent. Ten days later, when there were no signs of tetany, it was 71 volume per cent.

CASE 5—History—M J H (Med No 16151), a housewife, aged 29, entered the hospital May 28, 1921, with toxemia of pregnancy, greatly reduced renal function, severe acidosis and frequent vomiting. Plasma carbon dioxide capacity was 19.5 volume per cent.

Course—Because of this acidosis, 500 c.c. of 4 per cent sodium bicarbonate solution was given intravenously and Murphy drip with 2 per cent sodium bicarbonate was started, followed by a rise of carbon dioxide capacity to 27 volume per cent. The intravenous injection of sodium was repeated, vomiting decreased, and 2 gm. of sodium bicarbonate was given by mouth every two hours. Three days after admission to the hospital the plasma carbon dioxide capacity was 67.5 volume per cent. The following day the patient developed typical carpal spasm of tetany, the forearms were flexed and folded over the chest, the wrists were moderately flexed, and the fingers partially flexed at the metacarpal phalangeal joints and extended at the interphalangeal joints, and the thumbs were adducted. There were also occasional twitchings of the muscles about the mouth. Plasma carbon dioxide capacity at this time was 87 volume per cent. Administration of alkali was discontinued and spontaneous spasm soon disappeared, but a markedly positive Trousseau sign of tetany could be elicited from then until death five days later. The plasma carbon dioxide capacity remained above normal, and several hours before death was still 79.5 volume per cent.

CASE 6—History—E M (Med No 16492), a pupil nurse, aged 20, of neurotic temperament, became hysterical after failing to pass her examinations, and began to breathe very rapidly and deeply. She then complained of numbness and tingling in the fingers. After stopping the hyperpnea, the sensations disappeared. Later in the day the rapid deep breathing returned, tingling in the fingers started again, and the hands rather suddenly became spastic, the fingers and hands being flexed, and the phalanges extended. The arms soon became flexed at the elbows, and there was a sense of tightness in the abdominal muscles. She was persuaded to breathe quietly, and the spasm subsided in a few minutes. The following morning there was a mild recurrence of the hyperpnea, with tingling in the fingers, but no spontaneous spasm.

Examination—Compressing the arms above the elbow for a few minutes resulted in a typical spasm of tetany in the hands. There was no Chvostek sign. She soon began to breathe quietly and all signs of tetany disappeared. The plasma carbon dioxide capacity during the attacks was not determined, but there is every reason to believe that it would have been low, due to the decrease of carbon dioxide in the blood accompanying overventilation. Grant and Goldman³ found symptoms of tetany identical with those in this patient in voluntary forced respiration. Carbon dioxide is "washed" out of the blood, leaving a relative excess of sodium bicarbonate, and in the reestablishment of the $\frac{N_2H \cdot CO_3}{H_2 \cdot CO_3}$ ratio, alkali passes out of the plasma into the tissues and into the urine, resulting in a reduced plasma carbon dioxide capacity.

SUMMARY

1 The occurrence of tetany in various disorders of the body is discussed. These disorders may be divided into two groups (a) pyloric obstruction, hyperpnea and overdosage with sodium bicarbonate, which

have in common a disturbance of the acid-base equilibrium, due to an increase in the ratio of sodium bicarbonate to carbonic acid ($\text{NaHCO}_3/\text{H}_2\text{CO}_3$) in the blood (b) Infantile tetany and parathyroid tetany, in which there is a calcium deficiency in the blood The theory of Freudenberg and Gyorgy, which attempts to explain all tetany as being due to a deficiency of calcium in the tissues, is discussed

2 Six cases of tetany in adults are reported These are all of the type in which there is an acid-base disturbance Three cases occurred in obstruction of the stomach In two of these the plasma carbon dioxide capacity was determined, and found greatly increased In one the blood chloride was determined and found markedly decreased Serum calcium, determined in this case, was in the upper limits of normal These results corroborate in the human the experimental findings of investigators in animals Two cases resulted from overdosage with sodium bicarbonate, and one occurred in hysterical hyperpnea¹⁴

14 After this paper was written Freudenberg and Gyorgy [*Klinische Wchnschr* **1** 410, 1922] reported cases of infantile tetany in which the symptoms rapidly disappeared following ingestion of from 3 to 7 gm ammonium chloride per day The use of this drug was suggested by the recent work of Haldane (*J Physiol* **55** 265, 1921), who found that the administration of large doses of ammonium chloride by mouth caused an acidosis in the human, apparently by the formation of urea and hydrochloric acid The symptomatic cure of infantile tetany by the drug is, therefore, strong evidence in favor of the view that there is an "alkalosis" in this condition

THE BLOOD PRESSURE OF NORMAL CANTONESE STUDENTS

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It has been a common observation of my colleagues and myself that the blood pressure of Chinese patients in the Canton Hospital usually registered below the normal recognized for the peoples of Europe and North America. It was, therefore, decided to make a systematic study of the pressure of normal Cantonese young men with the idea of determining the average norm for that race.

Various methods have been employed by research workers in order to determine the blood pressure. Perhaps, the most accurate data are those obtained by the Erlanger sphygmomanometer. In reviewing the literature we find, however, that the mercury instruments are those most generally employed. The aneroid Tycos instrument is preferred by some.

METHODS OF READING

In the earlier reports, the systolic pressure was determined by palpation of the pulse. The diastolic and pulse pressures cannot be determined accurately by this method.

More recently as a result of the suggestion of Korotkoff,¹ the auscultatory method was introduced for reading the pressure. By this method it is universally recognized that the first sound or beginning of the first phase represents the systolic pressure. In regard to the diastolic reading, there has been considerable difference of opinion. Barach and Marks² in a series of observations on healthy students read the diastolic pressure in the fourth phase with some and with others at the disappearance of all sound, or the fifth phase. The difference in readings at these two points was generally about 5 mm of mercury, but was as great as 10 mm in some. Judson and Nicholson³ recommend reading at the fourth phase. They claim that by reading at the fifth phase, there is an error of from 11 to 20 mm.

Murray⁴ also agrees that the diastolic pressure must not be read below the fourth phase. Warfield,⁵ however, states that the fifth phase may be used, and from the fourth to the fifth there is usually only from 4 to 6 mm difference.

1 Korotkoff Tr Imp Acad Med, St Petersburg, **15** 365, 1905

2 Barach, J H, and Marks, W L Arch Int Med **13** 648 (May) 1914

3 Judson, C F, and Nicholson, P Am J Dis Child **8** 257 (Aug) 1914

4 Murray, J R Brit M J **1** 697, 1914

5 Warfield, Louis M Am J M Sc **154** 414, 1917

According to Weyssse and Lutz,⁶ "Fischer (1908), Lang and Manswetowa (1908), Van Westenrijk (1908) and Warfield (1912) consider the beginning of the fourth phase as the auscultatory index for minimum pressure, while Ettinger (1907), Gittings (1910) and Goodman and A A Howell (1910) consider the fifth phase as the correct index." They conclude that "Since the onset of the fourth phase is coincident with the marked decrease in amplitude of the oscillations recorded by the Erlanger sphygmomanometer, it should be considered as the index of minimum blood pressure."

Finally, MacKenzie,⁷ quoting W A Jaquith, states that "The fourth point is shown to be more liable to incorrect estimation than the fifth," and he further adds that the fifth point thus appears to be the one at which, for the sake of uniformity and accuracy, we should ask an examiner to take the diastolic reading. In one set of readings the average difference between points four and five was only 6 mm in 1,835 examinations.

In view of these conflicting opinions, we have generally advised those not very well accustomed to the use of the sphygmomanometer, to read the diastolic pressure at the disappearance of all sound. In the statistics given herewith, however, we have generally used the fourth phase for recording diastolic pressure, though, in some cases probably, the mercury was read between the fourth and fifth phases.

THE NORMAL PRESSURE

For comparative purposes, the first essential is the determination of a normal average in some particular race.

Systolic Pressure—It has been asserted⁸ that the normal systolic pressure for any age is roughly 100 mm of mercury, plus a figure represented by the age in question. The difficulty with much of the data at hand is that it deals with special groups of individuals, as, for example, insured persons, athletes, army recruits, etc.

One of the most thorough of the earlier investigations was Woley's⁹ study of 1,000 healthy persons ranging from 15 to 65 years of age. The palpatory method was used and for the whole series he obtained an average of 127.5 mm for males and 120 mm for females. For the period from 15 to 30 years of age, the average was 122 mm.

McCrae¹⁰ states that for adults a systolic pressure of 110 or less may be called "low blood pressure." Fraser and Cowell¹¹ made a study of the pressure in normal soldiers and obtained an average of systolic from 110 to 120 mm.

6 Weyssse, A W, and Lutz B R. *Am J Physiol* **32** 427, 1913.

7 MacKenzie, L F. *Med Rec* **97** 1029, 1920.

8 Editorial. *J A M A* **75** 1650 (Dec 11) 1920.

9 Woley, H P. *J A M A* **55** 121 (July 9) 1910.

10 McCrae, T M. *Clin N America* **3** 1177 (March) 1920.

11 Fraser, J, and Cowell E M. *J A M A* **70** 520 (Feb 23) 1918.

Barach and Marks² examined a group of healthy male students, mostly from 15 to 25 years of age. The systolic pressure varied from 90 to 200 mm, but the majority were between 110 and 140 mm. In more than 600 cases, 204 were recorded between 120 and 130 mm of mercury. In 90 per cent the systolic pressure was less than 150 mm.

Lee¹² examined Harvard freshmen. The average age was 18 years, the average height 5 feet 8 inches, and the average weight, stripped, 143 pounds. The average systolic pressure was 120 mm and only 12.8 per cent showed a systolic pressure above 140.

The Diastolic and Pulse Pressures—The diastolic and pulse pressures were not recorded in the older studies and accurate data have only in recent years been obtained, especially since the introduction of the auscultatory method of reading. MacWilliam and Melvin,¹³ in a series of healthy young adults, found the average diastolic pressure to be 65 mm with a range from 50 to 80 mm. The average pulse pressure was 46 mm. Barach and Marks,² in their series, found that in 92 per cent, the diastolic pressure did not exceed 100 mm and readings from 30 to 130 mm were obtained. The great majority, however, ranged from 70 to 100 mm. The pulse pressure ranged from 20 to 70 mm in 88 per cent of their cases, a large proportion ranging from 30 to 60 mm. The extreme limits of pulse pressure were from 5 to 100 mm.

In Lee's study,¹² only five subjects had a diastolic pressure higher than 100 mm, the average being 80 mm.

Warfield⁵ gives a normal variation for the pulse pressure of from 30 to 50 mm.

Fraser and Cowell,¹¹ in their series of soldiers, give from 70 to 80 mm for the diastolic average and 40 mm as the average pulse pressure.

Influence of Age on Blood Pressure—In dealing with younger subjects age is such an important factor that disregard of it renders statistics valueless. Wolfensohn-Kriss¹⁴ determined the systolic pressure of healthy children (Table 1), and concludes that the pressure increases with age, height and weight. In children of the same age, taller and heavier subjects gave higher pressure readings than shorter and lighter subjects. In boys and girls of the same weight, the pressure readings for boys were slightly higher than those for girls, but, in general, she concludes that there is practically no difference noted for boys and girls of the same heights and weights (Tables 4 and 5).

Fisher¹⁵ gives the average systolic pressure for accepted insurance risks at from 15 to 39 years (Table 1).

12 Lee, R. I. Boston M. & S. J. **173** 541, 1915.

13 MacWilliam, J. A., and Melvin, G. S. Brit. M. J. **1** 693, 1914.

14 Wolfensohn-Kriss, P. Arch. f. Kinderh. **53** 332, 1910.

15 Fisher, J. W. Proc. Assn. Life Ins. Med. Directors N. America, **393**, 1912.

TABLE 1—THE SYSTOLIC BLOOD PRESSURE ACCORDING TO AGE OF DIFFERENT RACES BY VARIOUS OBSERVERS

Age	Wolfen- sohn- Kriess ¹⁴	Fisher ¹⁵	Katzen- berger Several Observers ¹⁶	Judson and Nichol- son ³	Faught ¹⁸	Alvarez ¹⁹	Hunter ²¹	Willits	Faber and James ²²	McCay ²⁸ Bengali	Mus- grave and Sison ²⁹ Filip- inos	Cham- berlain ³⁰ White Men in Philip- pines	Cham- berlain ³⁰ Filip- pines	Con- cepcion and Bu- latao ³¹ Filip- pines	Trimble, Chinese	Whyte, Chinese	Cad- bury, Can- tonese
6			95	93 8	80-100				94 5								65
7	90		103	87 9					97 3								80
8			99	93	90-105				99 2								84
9	90		97	91 7					100 9								80
10			104	99					102 4								83
11	98		107	95 8					104 1								88
12			108	99 9	95-110				105 9								89
13	99		114	104					107 6								97
14				105 8	95-115				110 0								97
15	101			99 6					112 2							99	100
16		118			95 120	126	120	120	115 3							104	100
17	113					128							112 8	110 7		104	100
18						127									97	108	102
19						126										116	105
20						126										111	103
21						125										113	102
22		123 5				126	122			90-105			115 4			122	108
23						126											93
24						130										130*	103
25						126										130*	100
26														111 9	90		93*
27		125 6					123										110*
28						126		124					117				
29											108						95*
30																	103*
31							124										130*
32		125 5				126		124					116 7	118 8	101		
33													116 9				
34																	

* Only one case for this age was reported

Katzenberger¹⁶ gives the general average systolic pressures of eight other observers and her own (Table 1) for different ages

According to Judson and Nicholson,³ in a study of 1,344 children, the widest variations occur from the tenth to the fourteenth year. The systolic pressure shows a gradual rise from the third to the tenth year and from 10 to 14 there is a more abrupt rise. The systolic pressure varies from 91 mm in the fourth year to 105.5 mm in the fourteenth year. There is no arithmetic increase from year to year, from 4 to 14 there being only a total rise of 14 mm.

TABLE 2—DIASTOLIC PRESSURE BY AGE

Age	Judson and Nicholson ³	Fabr and James ²²	Concepción and Bulatao, ³¹ Filipinos	Trimble, Chinese	Whyte, Chinese	Cadbury, Chinese
6	63.5	64				
7	64.2	65.4				35
8	59.6	66.7				50
9	62.2	67.8				53
10	64.6	68.9				51
11	62.3	69.9				50
12	59.6	71.1				55
13	63.2	71.9				56
14	63.7	73.3				59
15	61.8	74.6			63	60
16		75.8			70	60
17					70	63
18			77.6		68	64
19				55	77	65
20					74	62
21					72	63
22					78	59
23						59
24					76*	57
25			76.6	56	72*	73
26						70*
27						85*
28						
29						70*
30						75*
31-40			80.3	62		80* and 50*

* One case only

There is little increase of the diastolic pressure, so that the pulse pressure increases more in proportion than the systolic pressure.

Observations were made by the pith ball oscillation method, a modified Erlanger apparatus and the ordinary mercury sphygmomanometer, using auscultation for reading the pressure. The observations by these methods differed slightly. In Tables 2 and 3 are recorded only the results obtained by auscultation.

Bing¹⁷ examined 138 men, all inmates of an institutional "home," and found that the systolic pressure ranged from 115 to 145 mm. He states that the normal systolic blood pressure seems to be from 100 to 130 mm.

¹⁶ Katzenberger, A. *Ztschr f Kinder* 9 167, 1913

¹⁷ Bing, H. I. *Ugesk f Laeger*, 77 923, 1915, abstr. *J A M A* 65 468 (July 31) 1915

Faught's ¹⁸ averages for systolic pressure cover the ages 6 to 17 years (Table 1)

A very careful analysis of the systolic blood pressure readings of all freshmen entering the University of California has been contributed by Alvarez ¹⁹ The readings for 2,930 males were taken with the men lying down The curve of average pressure does not rise steadily, but drops between ages 17 and 21 The upper normal limit for men he places at 130 mm Fifty per cent of the readings were between 116.5 and 136.5 (Table 1)

TABLE 3—PULSE PRESSURE BY AGE

Age	Judson and Nicholson ⁷	Faber and James ²²	Concepción and Bulatao, ²¹ Filipinos	Trimble, Chinese	Whyte Chinese	Cadbury, Chinese
6	30.3	31.1				
7	22.7	32				30
8	33.4	33.1				28
9	29.5	33.8				31
10	31.4	33.9				29
11	33.5	34.6				33
12	40.3	35.2				33
13	30.8	36.1				33
14	42.1	37.5				35
15	37.7	38.5			36	36
16		39.6			31	41
17					35	37
18			33.1	40	39	39
19					39	40
20					37	41
21					42	40
22					41	42
23						34
24			35.3	31	54*	40
25					58*	27
26						25*
27						25*
28						
29						25*
30						30*
31-40			38.5	39		50* and 40*

* One case only

According to Hunter and Rogers,²⁰ men over weight average a higher systolic pressure than men under weight A variation of 15 mm below the average or 15 mm above is within normal limits

One of the most extensive series of studies of the systolic pressure is that given by Hunter ²¹ on 67,000 life insurance cases (Table 1)

MacKenzie ⁷ states that the systolic pressure increases with increased weight, disregarding age and height The latter has little effect There is little change in the pulse pressure until after 40 years of age

For the period of from 15 to 29 years, the average systolic pressure is 122 mm, the diastolic 85 mm and pulse pressure 43 mm From

18 Faught, F. A. Blood Pressure from the Clinical Standpoint, Ed. 2 W. B. Saunders Company, Philadelphia, 1916

19 Alvarez, W. C. Arch. Int. Med. **26** 381 (Sept.) 1920

20 Hunter, A., and Rogers, O. H. Proc. Assn. Life Ins. Med. Directors N. America **6** 92, 1919

21 Hunter, A. Proc. Assn. Life Ins. Med. Directors N. America **7** 153, 1920

30 to 44 years of age, the systolic pressure is 125 mm, diastolic, 88 mm, and pulse pressure 43 mm. Any diastolic pressure at any age, under 60 mm or over 103 mm is abnormal if constant.

Pulse pressures over 60 mm or under 25 mm are cause for close scrutiny of every other feature.

According to a leaflet signed by Dr Charles H Willits, medical director of the Provident Life and Trust Company, Philadelphia, and issued to medical examiners, accepted risks between ages 15 and 60 years should have an average systolic blood pressure between 120 and 135 mm (Table 1). A normal diastolic pressure may be between 60 and 105 mm.

Faber and James²² studied the pressure in 651 boys and 450 girls aged from 3 to 17. The subjects were normal, mostly school children. They state that age is as satisfactory as any factor, such as height or weight, in determining the normal pressure. In order to smooth out the curves, three ages were grouped together. Thus for age 6, the averages for 5, 6 and 7 were added together and divided by 3. In Tables 1, 2 and 3 we record the readings for the boys only.

Other Factors Causing a Normal Variation in Blood Pressure—It is well known that many factors cause a normal variation in blood pressure. Thus Katzenberger¹⁶ in a series of observations noted that the blood pressure tends to fall as the rate of the pulse increases. The lower blood pressure in young children is to be explained by the undeveloped condition of the heart and blood vessels. As height and weight increase, the systolic pressure increases also. Therefore the pressure of children living under good conditions is higher than in children placed in bad conditions. Boys have higher pressure due to their greater size. Sleep causes a fall in pressure. Position, psychic phenomena, time of day, taking food or fluid, movements of the body, respiration and bathing all affect the pressure.

Faught¹⁸ observed that with puberty, adult pressure is established. There is a fall of pressure with increased altitude. In persons of neurotic temperament, according to Goodman,²³ the blood pressure is likely to be elevated.

Lowered pressure is said²⁴ to be the result of a weakened heart, as in convalescence from disease, and also as the result of a lack of dynamic force in the individual.

Fraser and Cowell¹¹ noted that in soldiers actually engaged in fighting, especially infantrymen, the average systolic pressure worked out higher than among men in the same regiment in support, where they were only exposed to occasional fire. The increased pressure of the

22 Faber, H K, and James, C A. *Am J Dis Child* **22** 7 (July) 1921.

23 Goodman, E H. *Blood Pressure in Medicine and Surgery*, Lea & Febiger, Philadelphia, 1914, p 64.

24 Moulton, R H. *The Forecast*, p 171 (Sept) 1921.

fighting man tended to drop quickly when he was resting away from the firing line, so that a systolic pressure of 140 mm might fall to 110 or even to 100 mm

The influence of age has been already referred to and Norris²⁵ states that preceding the onset of puberty, there is a tendency toward a fall of pressure; during pubescence there is a period of increased pressure which is, in turn, followed by a slight decrease after puberty has been established

The rate of the pulse is thought by Woley⁹ to be a factor. In cases with a pulse under 65, he found the pressure to average 123, while, if the pulse was over 85, the pressure reached 130 mm

TABLE 4—SYSTOLIC PRESSURE ACCORDING TO HEIGHT

Height in Centimeters	Wolfensohn-Kriss ¹⁴	Michael ²⁶	Chamberlain ³⁰ White Men in Tropics	Cadbury, Chinese
90-100	85	99		70
101-110	89			65
111-120	90			82
121-130	93	112		84
131-140	95			87
141-150	101	118		96
151-160	104			100
161-170	110	125	$\left\{ \begin{array}{l} 117.9^* \\ 114.7 \\ 116 \\ 115.5 \\ 116.2 \end{array} \right\}$	102
171-180			$\left\{ \begin{array}{l} 115.7 \\ 116.2 \\ 117.9 \end{array} \right\}$	105
181-190			$\left\{ \begin{array}{l} 119.3 \\ 120.6 \end{array} \right\}$	105

* Under 162.5 cm

The effects of height and weight have already been referred to. These factors have been especially considered by Michael²⁶. She studied 128 normal children and found that there was a regular rise in systolic pressure with an increase in height and weight. This is also confirmed by the work of Wolfensohn-Kriss¹⁴ and Chamberlain³⁰ (Tables 4 and 5).

The effects of climate are referred to by Castellani and Chalmers²⁷ as lowering the tension of the pulse, with dilatation of peripheral vessels and increased elasticity of the pulse.

25 Norris, G. W. Blood Pressure, Lea & Febiger, 1917, p. 378

26 Michael, May. Am J Dis Child 1:272 (March) 1911

27 Castellani & Chalmers. Manual of Tropical Medicine, Balliere, Tindall & Cox, London, 1919, p. 75

Variations in Blood Pressure by Race—We come now to the question of racial variations. But little mention has been found of variations because of race in the textbooks on blood pressure, and we have been able to find only a few references in literature.

McCay²⁸ studied the blood pressure of more than 500 adult male Bengalis, aged from 20 to 25 years. They were Hindus from Lower Bengal. The Riva-Rocci instrument was used with a broad armlet. The systolic pressure only was determined, by palpation, with the patient sitting. The average pressure was found according to one report to be from 83 to 118 mm of mercury, but, in the later report, he states it was from 90 to 105 mm or generally just under 100 mm.

To explain this low pressure, McCay considers climatic conditions are not the chief cause, because Europeans living in Calcutta did not show this low pressure, they averaging from 115 to 130 mm of mercury. As the capacity for muscular work in Europeans is superior, we may

TABLE 5—SYSTOLIC PRESSURE ACCORDING TO WEIGHT

Weight in Kg	Wolfensohn Kriss ¹⁴	Michael ²⁶	Cadbury, Chinese
16-20	82	95	81
21-25	92	100	83
26-30	94	107	87
31-35	95	112	94
36-40	99	116	96
41-45	103	122	100
46-50	111	126	101
51-55	112		104
56-60			106
61-65			106

assume that they also have superior muscular power in both voluntary and involuntary groups.

The Filipino has been studied more carefully with regard to his blood pressure than other Oriental races. The first work was done by Musgrave and Sison²⁹. The study was made on ninety-seven Americans and Europeans and forty Filipinos, mostly students. The ages varied from 25 to 40 years. They concluded that the systolic pressure of persons living in the tropics is lower than the general averages given. The heart and blood vessels are not to blame. Variation in the volume and viscosity of the blood may be a factor. Anemia is not a cause. The most probable cause is the lowered peripheral resistance that occurs in the tropics²⁷. If this be true, then the lowered blood pressure may be explained in two ways: the secretory function of the skin is increased

²⁸ McCay, David. *Lancet* 1 1483, 1907, Scientific Memoirs, Govt of India, No 34 p 23, 1908.

²⁹ Musgrave, W. E., and Sison, A. G. *Philippine J. Sc.* B 5 325, 1910.

and probably the normal surface resistance and vasomotor tension necessary to produce the required surface heat of temperate climates is greatly diminished in the tropics, the year round

There are also to be considered the splanchnic influences which control vasomotor tone

For foreigners, the following pressure readings were obtained

Duration of Residence in Tropics	Systolic Pressure
1 month to 1 year	124 mm
1 year to 5 years	115 mm
5 years to 10 years	116 mm
Over 10 years	113 mm

Of the Filipinos, thirty males gave an average systolic pressure of 108 mm and nineteen females of 113 mm

A very extensive study was carried out by Chamberlain³⁰ He studied the systolic pressure of 1,042 healthy, white, American soldiers, aged mostly from 20 to 40 years, and 386 Filipinos representing various tribes, and including soldiers, laborers, servants and convicts Most of these were under 42 years of age Chamberlain assumes a normal of from 115 to 150 mm of mercury for men from 15 to 30 years of age, living in the temperate zone

In the Philippines, he finds the average pressure for white men at this age to be 115 and from 30 to 40 years of age to be 118 mm Seasonal changes and complexion—blond or brunet—did not affect the systolic pressure He suggests that there is a vasoconstriction of superficial blood vessels

For Filipinos between 15 and 40 years, Chamberlain found an average systolic pressure of from 115 to 116 mm He concludes that there is no essential difference from white men in the blood pressure (Table 1)

A later study of Filipinos has been made by Concepción and Bulatao,³¹ using an Erlanger sphygmomanometer Readings were obtained from 697 males and 218 females, varying in age from 15 to 87 years The males were chiefly convicts and medical students The females were also convicts and students The results may be found in Tables 1, 2 and 3 For the average age of males of 29.5 years and of females of 25.1 years, the average readings were as follows

	Males	Females
Systolic Pressure	115.6 mm	116 mm
Diastolic Pressure	79.1 mm	83.4 mm
Pulse Pressure	36.4 mm	32.6 mm

There is to be noted a general tendency for the systolic, diastolic and pulse pressures to ascend with age They conclude that, "The

30 Chamberlain, W. P. *Philippine J. Sc. B.* 6: 467, 1911

31 Concepción, I., and Bulatao, E. *Philippine J. Sc. B.* 11: 135, 1916

systolic pressures of Filipinos are very much lower than those of Americans living in temperate climates (Woley), but the same as those of Americans living in the tropics (Chamberlain) "

In sixty-five opium habitués the blood pressure was much below the average of other cases

Investigations of American Indians were carried on by Harley Stamp³² including tribes living in the arctic as well as the temperate zone He concludes that "the normal age charts of blood pressure records on the American Indian differ but slightly from those of the white man, except that there seems to be a uniform tendency to reduced blood pressure at or about 45 years "

Blood pressure in the Japanese has been studied by Tanemura³³ who examined 2,842 healthy male and 1,100 female Japanese The ages varied from 4 to 25 years He used a von Recklinghausen tonometer, reading by Korotkoff's auscultatory method The results were recorded in centimeters of water The average height for boys of 4 was 93 cm, for boys of 19, 160.3 cm The body weight was 13.6 kg for boys of 4 and 54.1 kg for men of 21 The annual increase in the blood pressure was particularly marked in boys from the thirteenth to the seventeenth years In general, the curve of rising blood pressure ran parallel with those of body height and weight

The normal pressure at 4 years of age for boys was systolic, 72 mm, diastolic, 49 mm of mercury (98 and 67 cm water) It rose gradually to systolic 122 mm, diastolic 83 mm of mercury (165 and 112 cm water) in men of 19

The pulse pressure rose from 23 mm of mercury (31 cm water) at 4 years to 40 mm of mercury (54.5 cm water) in men of 19

BLOOD PRESSURE IN CHINESE

Beyond the records of Chinese here collected, I know of no statistics on this race in the literature

A questionnaire was sent out to missionary physicians throughout China and answers giving records of normal persons were received from only three Drs C G Trimble, Duncan Whyte and H W Boyd Doctor Trimble sent in records for thirty-two normal male Chinese Twenty-four were from the province of Fukien, which lies between 23 and 29 degrees north latitude, and eight from other provinces of China The occupations of the Fukinese varied from that of student merchant, druggist, coolie, soldier, barber, shoemaker, baker, boat man, preacher and farmer The Pilling special sphygmomanometer was

³² Faught, F A 1 c, 18, p 161

³³ Tanemura, I Kyoto J M Sc 15 84, 1918, Abstr China M J 34 542, 1920

used with the auscultatory method. The ages varied from 18 to 43 years and the average pressures obtained were as follows: Systolic 100, diastolic, 61, pulse, 38 (Tables 1, 2 and 3)

The eight subjects from other provinces of China varied in age from 19 to 28 years. Four were from the province of Chihli, two from Shantung, one from Kiangsu and one from Hunan, all in Central or North China. The average pressures were as follows:

Systolic	106 mm
Diastolic	66 mm
Pulse	40 mm

Dr G. Duncan Whyte's studies were made on healthy students in Swatow, which is located in the northern part of Kwangtung Province. He employed the Faught instrument and the auscultatory method. There were eighty-five males varying in weight from 25.8 to 64.4 kg (57 to 142 pounds) and in height from 137 to 176 cm (54 to 69½ inches). The ages varied from 15 to 25 years. There were only two subjects over 22 years of age. For the other eighty-three men he obtained the following averages:

Systolic	109 mm
Diastolic	71 mm
Pulse	38 mm

For the pressures recorded for each age, see Tables 1, 2 and 3.

Dr H. W. Boyd, of Canton, studied fifteen men and ten women from the provinces of Kwangtung and Kwangsi. Their ages ranged from 18 to 54 years, averaging 28 years, and their occupations were those of farmer, mechanic, merchant, student, housewife, prostitute, nurse, druggist, soldier, physician and laboratory assistant. Their weights varied from 26.3 to 66.2 kg (58 to 146 pounds) and their heights from 139.7 to 182.8 cm. Doctor Boyd used a Tycos instrument with the auscultatory method. He obtained the following averages:

Systolic Pressure	107 mm
Diastolic Pressure	67 mm
Pulse Pressure	40 mm
Average Pulse Rate	81 mm

My investigation of the blood pressure of healthy Cantonese was conducted as part of a general program of determining the characteristics of normal Chinese.

The records were all obtained from healthy Chinese students of the two southern provinces of China known as Kwangtung and Kwangsi. Canton, the capital of Kwangtung, lies on latitude 23 degrees 06'1" north and the two provinces lie between 20 and 26 degrees north latitude.

It is well known that the Cantonese differ in many ways from the people of other parts of China. They are shorter, lighter and with smaller features. Unlike most people living in the tropics, they are noted for their energy and progressiveness.

All of my records were taken in the routine physical examination of 774 students of the Canton Christian College. These young men live in much better hygienic conditions than the average Chinese. They take part in athletic sports and eat a better quality of food. Their life is very similar to that of American boys.

All students with cardiac murmurs or other evidence of cardiac or pulmonary disease were excluded. My records are based therefore on the examinations of only healthy young men.

A Nicholson sphygmomanometer was used, employing the auscultatory method. A 14 cm. wide cuff was used on the right arm, with the subject sitting and resting his arm on a table.

The systolic reading was made at the first appearance of sound and the diastolic at the fourth phase, but, in the younger boys, the diastolic reading was often very indefinite. Taking the averages for certain age periods, we find as follows:

7 to 14 years	{ Systolic	83 mm
	{ Diastolic	51 mm
	{ Pulse	31 mm
15 to 20 years	{ Systolic	101 mm
	{ Diastolic	62 mm
	{ Pulse	39 mm
21 to 30 years	{ Systolic	101 mm
	{ Diastolic	68 mm
	{ Pulse	36 mm

By reference to Tables 1, 2, 3 and 6 the detailed figures may be observed.

There is very probably a slight error in the age factor in a few of the cases, since Chinese generally estimate their age as one year older because they count that they are one year old at birth. However, even by the most casual glance at the figures in Table 1, it is clearly evident that the Cantonese youth has normally a systolic pressure considerably lower than that found in Europeans and Americans. It follows closely Musgrave's figures for Filipinos, but is lower than that reported by Chamberlain and Concepción and Bulatao. It is also lower than the records for Japanese, but compares with what was found among Bengali.

Diastolic pressure is also lower than what has been recorded by other observers, but the pulse pressure is slightly higher than found in one of the studies of Filipinos.

Objection is taken sometimes to the misleading character of averages. We have, therefore, taken the systolic readings for ages 15 and 20 and

grouped them in their order of frequency. The average readings were 97 and 103, respectively. The percentages for different readings were as follows:

	Age 15	Age 20
71 to 80 mm Hg	12%	4%
81 to 90 mm Hg	31%	13%
91 to 100 mm Hg	19%	38%
101 to 110 mm Hg	31%	22%
111 to 120 mm Hg	6%	16%
121 to 130 mm Hg	1%	7%

Thus 81 per cent of the readings for age 15 were between 81 and 110 mm. For age 20, 60 per cent of the readings were between 91 and 110 mm.

TABLE 6—BLOOD PRESSURE OF HEALTHY MALE CHINESE STUDENTS OF THE CANTON CHRISTIAN COLLEGE

Age	No	Average Pressure			Systolic Pressure		Diastolic Pressure		Pulse Pressure		Average Rate of Pulse
		Systolic	Diastolic	Pulse	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	
7	2	95	35	30	70	60	40	30	30	30	78
8	11	80	50	28	95	60	60	35	40	20	80
9	18	81	53	31	100	60	75	35	50	15	92
10	28	80	51	29	110	60	70	35	50	15	90
11	31	83	50	33	100	65	75	30	45	10	85
12	48	88	55	33	115	65	75	20	60	15	81
13	47	89	56	33	105	75	70	40	50	15	85
14	63	97	59	35	125	75	85	30	65	15	84
15	90	97	60	36	130	75	80	35	70	15	82
16	101	100	60	41	130	70	85	35	70	10	83
17	97	100	63	37	130	75	95	40	70	10	83
18	81	102	61	39	130	75	85	45	70	10	82
19	65	105	65	40	130	70	80	45	65	10	81
20	46	103	62	41	125	85	80	50	65	20	78
21	18	102	63	40	125	85	80	50	65	20	80
22	13	108	59	42	155	85	80	45	65	20	81
23	5	93	59	34	110	80	65	53	57	15	78
24	2	103	57	40	105	100	60	55	40	40	60
25	2	100	73	27	100	100	80	65	35	20	77
26	1	95	70	25							72
27	1	110	85	25							61
29	1	95	70	25							88
30	1	105	75	30							72
31	1	130	80	50							81
36	1	90	50	40							72

Following Wolfensohn-Küss and Michael, I have estimated the blood pressure in accordance with weight (Tables 5 and 7). Here the age factor was not involved, except that all measurements were made in male subjects from 7 to 36 years of age.

The systolic pressure shows an increase from 81 mm in boys weighing from 16 to 20 kg to 106 mm in young men of 61 to 65 kg weight or an increase of 25 mm. The diastolic pressure shows an increase of 15 mm and the pulse pressure a much less marked increase.

Wolfensohn-Küss' figures closely parallel my own up to the 40 to 45 kg limit. After that, her records are higher. Michael, on the other hand, gives considerably higher readings throughout the series.

If height is taken as the standard for estimating the pressure, there is also found to be a progressive increase as the subject grows (Tables 4 and 8)

Thus between the 101 to 110 cm group and the 171 to 180 cm group, the systolic pressure rises 40 mm, the diastolic 25 mm and the pulse pressure 16 mm

Comparing my readings with those of other observers, the Cantonese shows a marked inferiority in blood pressure taken with reference to his height

TABLE 7—AVERAGE BLOOD PRESSURE OF CANTONESE MALES ACCORDING TO THEIR WEIGHT

Weight in Kg	Number	Average Systolic	Average Diastolic	Average Pulse
11-15	1	60	30	30
16-20	30	81	51	29
21-25	66	83	51	32
26-30	85	87	55	32
31-35	70	94	60	34
36-40	67	96	59	37
41-45	141	100	60	40
46-50	160	101	63	32
51-55	107	104	64	40
56-60	35	106	65	41
61-65	9	108	66	41

TABLE 8—AVERAGE BLOOD PRESSURE OF CANTONESE MALES ACCORDING TO THEIR HEIGHT

Height in Cm	Number	Average Systolic	Average Diastolic	Average Pulse
90-100	1	70	40	30
101-110	3	65	41	23
111-120	27	82	50	31
121-130	68	84	52	32
131-140	89	87	55	32
141-150	93	96	59	37
151-160	200	100	61	39
161-170	256	102	63	39
171-180	32	105	66	39
181-190	1	105	70	35

DISCUSSION

It thus appears that the systolic blood pressure of Cantonese and other Chinese young men from the South of China averages from 20 to 30 mm of mercury less than the normal for people in Europe and North America. Correspondingly low systolic pressure has been observed among Bengali and Filipinos.

The diastolic pressure of the Chinese is also lower than the generally accepted normal, but by only 10 to 20 mm. The Filipinos' diastolic pressure seems to be higher.

The average pulse pressure shows little variation from the generally accepted normal, and is, therefore, relatively high.

In our studies there is a regular arithmetic increase of systolic and diastolic pressure values from 7 to 22 years of age. A less regular increase is observed in the pulse pressure.

In this connection it is a remarkable fact that hypertension as a pathological condition in Chinese is very unusual. In an extensive medical practice of more than twelve years in Canton, I have rarely met with hypertension, either with or without signs of nephritis, although chronic Bright's disease is very common. When met with, marked hypertension has generally been associated with aortic valvular disease of the heart. Other observers in Canton have confirmed my findings.

In looking for a possible explanation, the following suggestions have come to me: (1) Use of opium, (2) decreased capacity for muscular effort, causing a decrease in muscle tone, (3) small stature and lighter weight, (4) deficient suprarenal or other hormones in the body, producing a lack of dynamic force, (5) the large vegetable diet. A Chinese subsists chiefly on rice, with only minute amounts of meat. (6) Simplicity of life, and absence of nervous strain, (7) effects of the tropical climate causing (a) constant dilatation of the peripheral blood vessels, (b) the secretory function of the skin is increased and probably the normal surface resistance and vasomotor tension necessary to produce the required surface heat of temperate climates is greatly diminished in the tropics the year round, (c) splanchnic influences. The vasomotor tone of the splanchnic system has a marked effect on motor tone, (d) a vasoconstriction of the superficial blood vessels, (e) variations in the volume and viscosity of the blood.

In my studies of the Cantonese youth, I can exclude Numbers 1 and 2 as possible factors. Number 3 is applicable, as my studies prove that the Cantonese is shorter in stature and of lighter weight than American and European youth. Number 4 is at present based on theory, but I have seen no lack of vigor or dynamic force in our students.

It may be inferred that diet and the various factors listed under climate have a bearing on the phenomena.

CONCLUSION

A study of the blood pressure of 774 healthy, male, Cantonese youths shows that their average systolic, diastolic and, to a less degree, pulse pressures, are lower than the standards for European and American youth of corresponding age, weight or height.

RENAL FUNCTION AND THE AMOUNT OF FUNCTIONING TISSUE

THE RATIO UREA IN ONE HOUR'S URINE AFTER GIVING
 UREA IN 100 C C OF BLOOD
 UREA AND WATER *

T ADDIS, M D

SAN FRANCISCO

This is the first of a short series of papers, the outcome of an attempt to draw quantitative structural deductions from functional results. The few methods used are discussed and criticized only in reference to the question as to whether the results give information in regard to the amount of secreting tissue in the kidney. This narrow point of view has been adopted because the purpose of the inquiry is entirely utilitarian and clinical. All manifestations of renal function have an intrinsic interest from the standpoint of physiology, but it is maintained that only those from which we can draw quantitative conclusions about the amount of tissue in the kidney are of immediate and practical clinical importance.

Such an idea is foreign to nearly all the recent work on this subject. Nevertheless, from the time of Bright up to about the beginning of the last decade, the hope that functional methods might ultimately be used as a measure of the extent of a renal lesion was probably the main incentive to clinical investigation into the function of the kidney. But since Schlayer's papers were published, that is to say, during the very time when technical methods were so perfected as greatly to facilitate the mechanical side of the work, this hope appears to have been abandoned. Schlayer is largely responsible for this modern attitude of disillusion. He demonstrated that there was no quantitative relation between the function of the kidney, as he determined it, and the amount of damage it had suffered experimentally or through disease. But while he rejected the idea of drawing quantitative structural inferences from functional work, he believed that functional methods were of value in detecting, if not the amount, at least the location of disease in the kidney. He thought he could determine whether disease affected mainly the vessels or mainly the tubules. However, it was soon shown that it was impossible to make such a distinction by functional methods. This failure to draw even qualitative anatomic deductions from functional results had a marked psychologic effect, all the more, because, at the same time, the limitations of histologic methods were emphasized. Instances were cited in which no evidence of renal damage was obtained by microscopic examination although there had been obvious indications of a failure of renal function, and, on the other hand, cases were

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reported with apparently normal function in which gross manifestations of structural derangement were found. In view of all these facts, the tendency of clinical investigators has certainly been to give up what seemed to be a hopeless attempt, to take what they did have—the functional results—and to try to establish classification and treatment on a functional rather than on an anatomic basis.

This view will not be held permanently. At best it is only a confession of failure, the result of inadequacies in present day functional and histologic methods. It can serve only as a preparation for a renewed attempt on the problem of the relation between renal function and structure, the problem which Bright set before himself nearly a century ago.

Improvement in functional methods has been mainly technical. We can now measure more easily, and also more accurately, the amounts of various substances eliminated by the kidney. But in other respects there has been little change. In particular, a fundamental principle applicable to all functional methods, when they are to be used for structural deductions, has been neglected almost entirely. Unless the functional manifestation is the maximal effort of which the organ to be tested is capable, no structural inferences can be drawn from it. For instance, it might be possible, from a measurement of the force exerted, to make a fairly accurate prediction as to the amount of muscular tissue concerned in some action, such as weight lifting—but only if the effort put forth were the greatest the muscles could perform. Thus, two different amounts of muscle tissue might both raise a 10 pound weight. No deduction as to their relative size could be made. But if it were to be found that in one case 50 pounds was all that could be lifted, while in the other case 100 pounds was the maximum, it would be legitimate to conclude, other things being equal, that one was twice as large as the other. In the kidney also the functional output must be at a maximum if quantitative deductions in regard to the amount of the secreting tissue are to be drawn.

In the above example the deduction as to the amount of muscular tissue from the functional result would be valid only if the conditions were such that extramuscular factors were equally operative. So, also, if renal function is to be used as a measure of the amount of secreting tissue, the extrarenal circulatory and nervous factors concerned in excretion must be uniform.

THE UREA RATIO TEST

The Ratio $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 C c of blood}}$ after giving urea and water

The development and some of the theoretic aspects of this test were dealt with in 1917¹. Since then the technic has been modified as a

¹ Addis J Urol 1 263 1917

result of further work on animals² and on man³ In its present form the method has been in use for two years in clinical work on Bright's disease, and it seems unlikely that any further considerable change will be required, although much remains to be done in regard to the establishment of standards of normality Only the practical application of the test will be dealt with in this paper

Two essential conditions are required One is that the kidney should be placed under circumstances which call for great activity in urea excretion The other is that there should be an absence of certain specific renal stimulants and depressants The first is met by the administration of an amount of urea which will raise the concentration of urea in the blood reaching the kidney, while at the same time a diuresis is induced by water drinking The second is fulfilled if the test is carried out in the morning, before the subject has taken food, and if the collections of urine and blood are not commenced until three hours after the urea has been taken

The details of the procedure used in clinical work are as follows At 6 a m the patient slowly drinks about 1,000 c c water in which urea is dissolved When the blood urea concentration is between 15 and 25 mg per hundred c c, 30 gm urea are given If the blood concentration is already as high as 60 mg of urea per hundred c c, no urea need be taken At intermediate blood urea levels appropriate quantities of urea are administered, so that when the first blood is collected it should have a concentration of between 60 and 90 mg of urea per hundred c c At 7 a m, and every hour thereafter until 11 a m, the patient drinks two glasses of water No breakfast is given Urine is voided every hour, but at 9 a m, the time at which urination is completed is noted to within thirty seconds, and at 10 a m, 11 a m and 12 noon urine is passed directly into special bottles and the exact time noted The patient must be instructed to make each voiding as complete as possible, and to take the time at the end, and not at the beginning of urination For women a special commode is used with a large funnel emptying into a removable bottle Blood is obtained at the middle of each of the three hourly periods over which urine is collected The urea content of these urine and blood specimens must be estimated with a high degree of accuracy, for even small errors may markedly influence the ratio if they happen to be in opposite directions for the blood and for the urine

When these conditions are observed the rate of urea excretion is governed by only two factors, the concentration of urea in the blood

2 Addis Barnett and Shevky *Am J Physiol* **46** 1, 22 39, 52, 1918 Addis, Shevky and Bevier *Am J Physiol* **46** 11, 129, 1918 Addis, Foster and Barnett *Am J Physiol* **46** 84, 1918

3 Addis and Drury *Proc Soc Exper Biol & Med* **23** 24, 1920

and the amount of secreting tissue in the kidney. Since the concentration of urea in the blood is determined, it follows that the ratio $\frac{\text{rate of urea excretion}}{\text{urea in 100 cc of blood}}$, or as we measure it, $\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc of blood}}$, is a measure of the amount of secreting tissue in the kidney.

When the amount of secreting tissue in the kidney is constant, the rate of urea excretion varies directly with the blood urea concentration. In the same normal adult individual the amount of renal tissue may be assumed to remain nearly constant, and if this statement is true, there should be a direct proportion between the amounts of urea in an hour's urine and the amounts of urea in 100 cc of blood, so

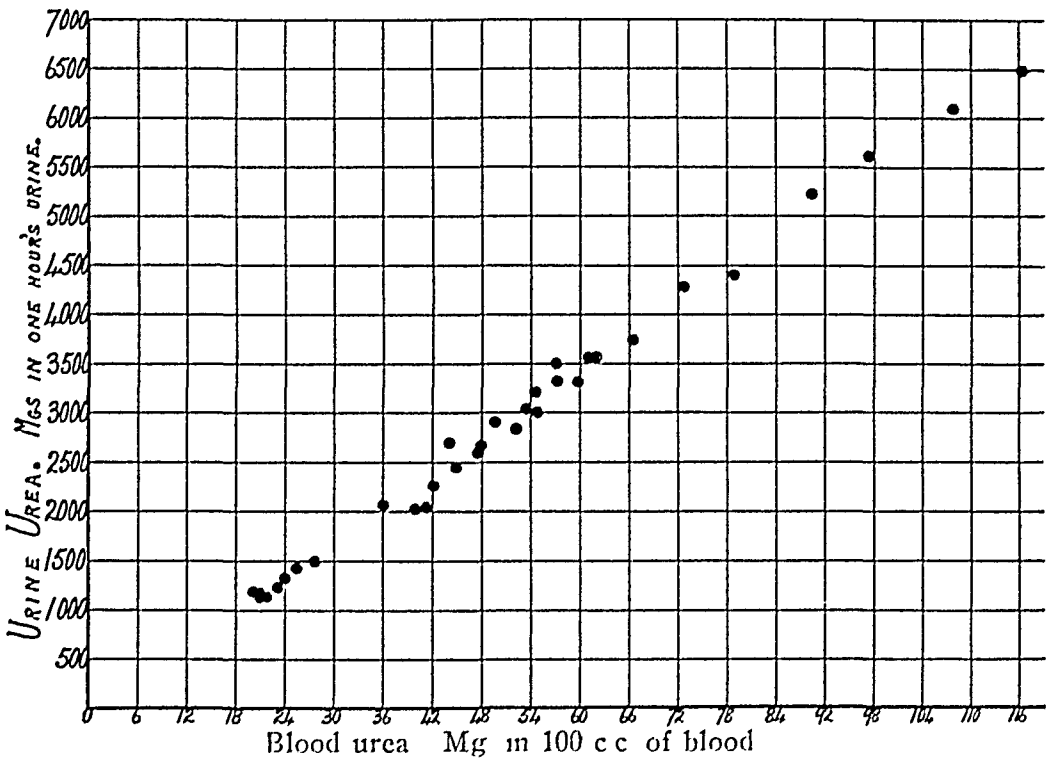


Fig 1—The amount of urea in one hour's urine is directly proportional to the amount of urea in 100 cc of blood, when the amount of renal tissue is constant, and when certain conditions are observed. Observations on the same subject at different levels of blood urea concentration.

that the rates plotted against their respective blood urea concentrations should fall in a straight line. Figure 1 shows a series of hourly rates measured in the same individual. The blood urea concentrations were varied by administering varying quantities of urea.

These experiments show that when the amount of renal tissue is constant there is a direct relation between the rate of urea excretion and the blood urea concentration, so that changes in the level of urea concentration in the blood between 20 and 120 mg are associated with corresponding changes in the rate of urea excretion.

It should be emphasized that this is not a general law. It holds true only under the special and peculiar conditions which have been

outlined We have many rates, observed in the subject from whom the measurements shown in Figure 1 were obtained, which show how far the rate of urea excretion may vary from any direct relation with the blood urea concentration, and we have already given many instances of great variations in the rate in spite of a constant blood urea concentration⁴ These variations are of particular interest and importance as showing the high degree of adaptability inherent in the mode of action of the kidney, and its freedom from subjection to merely physical and mechanical conditions But when we wish to deduce the size of the kidney from its function, all this complex mechanism of adjustment, of concurrent or alternating inhibition and excitation, must be merged in the drive toward the maximum rate of excretion allowable under the circumstances The fact that such a direct relationship between blood concentration and rate of excretion can be demonstrated, is an indication that we have succeeded in attaining this unity of action, and that under these special conditions all the circulatory and nervous factors concerned in renal activity are working together towards one end

When the amount of renal tissue varies, the ratio $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c c of blood}}$ is directly proportional to the amount of secreting tissue in the kidney This again, of course, is no general law, but is true only under the specific conditions described The detailed proof will require much further work, but there is already sufficient evidence that it is at least approximately true It has already been shown, though at that time the conditions under which the ratio ought to be measured were only imperfectly understood, that the loss of renal substance involved in the removal of one kidney,⁵ or the variable loss arising from differing degrees of uranium intoxication,⁶ was revealed by the degree of depression in the ratio We are now engaged in a study of the relation between the weight of the kidneys and the magnitude of the ratio in rabbits It appears that in the rabbit every 10 gm of renal tissue—the average weight of both kidneys in a medium sized animal—will yield a ratio of approximately 1.75 In man the average weight of both kidneys is about 300 gm If there is a direct relation between the magnitude of the ratio and the size of the kidney, we should accordingly, expect to find that the average ratio in man was 1.75×30 , or 52.5 Our present average for normal adults is 50.4—a sufficiently close agreement

In Table 1 all the ratios obtained from normal persons under these conditions are given There are 163 in all The number of persons is

4 Addis and Watanabe J Biol Chem **27** 249, 1916

5 Addis and Watanabe J Biol Chem **28** 251, 1916

6 Watanabe, Oliver, and Addis J Exper M **28** 359, 1918

thirty-one. Almost all of them were medical students between 23 and 30 years of age. In a few cases the amount of urea taken varied, but in the great majority 30 gm were given. The average ratio is 50.4, the standard deviation ± 6.61 and the variability (the standard deviation as a percentage of the average) 13.1 per cent.

Part of the variability in the ratios obtained from different normal persons is no doubt due to differences in the amount of renal tissue

TABLE 1—RATIOS OBTAINED FROM NORMAL ADULTS AFTER ADMINISTRATION OF UREA AND WATER

Name	Ratio	Name	Ratio	Name	Ratio	Name	Ratio
Dru	56.9	Add	45.1	Geo	43.5	Nak	43.0
	58.8		45.4		42.0		48.0
	56.0		42.3		38.5		47.0
	58.4		44.0		39.7		45.0
	57.6		51.4				
	54.4		42.9	Jac	60.8	Ank	48.4
	53.0		45.6		60.8		48.8
	54.6		44.8		61.4		50.0
	57.7		43.5		54.9		
	58.5		50.9			War	45.9
	54.2		49.6	New	39.2		49.1
	54.0		43.3		39.2		51.0
	53.6		41.9		39.8		
	49.1		50.9		39.6	Dia	48.2
	50.4		47.8		38.3		45.5
	57.4		43.1		35.9		48.0
	55.3		45.3		38.5		
	53.4		49.3			Ves	46.7
	56.1		44.3	Pis	45.1		43.8
	55.0		50.7		58.7		53.8
	52.6		42.4		42.5		
	51.2				51.4	Dun	50.5
	55.2	Jen	54.1		55.3		48.5
	53.8		48.3		47.1		41.9
	58.4		51.1				
	57.4		46.6	Kol	60.7	Moo	50.0
	61.4				61.7		49.0
	58.5	Hun	58.4		57.6		46.1
	55.4		58.2		58.2		
	56.4				56.9	Bin	49.0
	57.6	Aze	55.9		54.2		52.3
	59.0		52.6		56.0		47.7
	61.1						
		Har	38.6	Col	66.5	Sea	54.5
Col	41.2		38.1		59.4		55.1
	45.6		36.7		65.9		55.9
	44.2						
	47.4	Chr	43.7			Kel	51.5
			48.6	Cim	72.4		51.6
Swe	45.9				47.8		
	49.6	Pro	46.3		44.8		
	45.8		54.0			Pie	51.1
			54.4				47.0
Sei	44.7			Mye	46.0		46.2
	49.7				48.0		
	50.2	Nor	53.2		48.5		
	55.6		56.9		39.5	Nap	73.0
	54.5		58.6		41.0		55.6
	56.1		64.8		40.0		54.6

they possess. The true variability, i. e., the fluctuations due to the influence of other physiologic factors than the size of the kidney and to errors in collection and chemical technic, can be gaged in a rough way from the variability of the ratio in a single person. We have thirty-three ratios in the subject Dru and the variability is only 5.1 per cent, as compared with 13.1 per cent in the group. Some means should be found whereby the effect of these variations in the amount

of renal tissue in normal persons could be discounted. It is highly desirable for adults, and in dealing with children it is absolutely necessary, for their ratios are, of course, much lower than those obtained from adults, so that no direct comparison is possible. There is no doubt some relation between body weight and renal weight, and in the case of children we correct the ratio by reference to a curve drawn from average figures given by Vierordt⁷ on the percentage of kidney weight to body weight at different ages. But we have not found any data from which the reliability of this correction can be calculated.

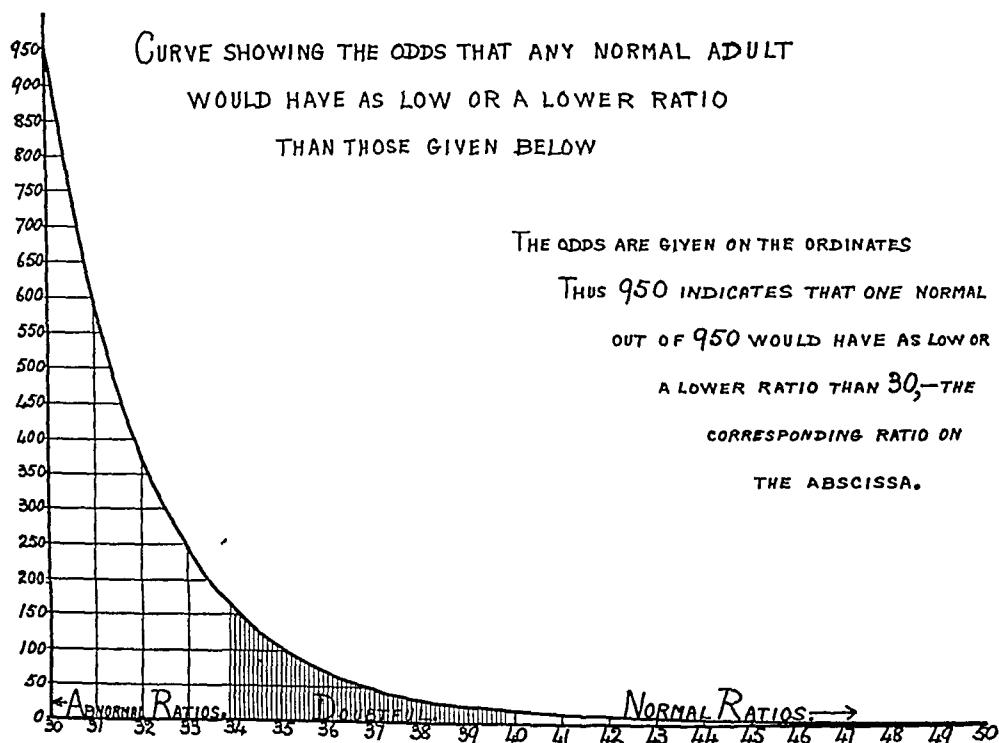


Fig 2—Provisional separation of ratio obtained in adult men or women into those which can be regarded as within the limits of normal variation (normal ratios), those which are regarded as beyond these limits (abnormal ratios), and those which cannot with any certainty be described as either normal or abnormal (doubtful ratios)

It seems likely that the relationship is far from being a close one. Warthin,⁸ who has been interested in this subject, thinks that the most reliable estimate of the range of variation in renal weight in adults is from 110 to 145 gm for the right kidney, and from 150 to 180 gm for the left, and he is impressed with the variability of the relation between kidney weight and body weight. Stewart⁹ recently published some figures which showed that kidney weight varied more

⁷ Vierordt Arch f Anat u Physiol Anat Abt, Suppl **62** 1890

⁸ Warthin, Practical Pathology, Ed 2, George Wahr Ann Arbor, Mich, p 155

⁹ Stewart, Am Physiol **57** 45, 1921

directly with body surface than with body weight. We are at present collecting data on this question. In the meantime, it seems preferable to use the ratio without attempting any correction for adults even though the range in which there is doubt as to whether normality or abnormality exists is thereby considerably widened. From the average and standard deviation of the ratios obtained from normal persons we have calculated the odds that any normal person would have as low or a lower ratio than those given in Table 2. The limits of the normal, the doubtful and the abnormal are provisionally and arbitrarily indicated. They are also shown in Figure 2.

Examples of the application of this method in clinical work will be given in a later paper of this series. We have found it of value in the diagnosis, prognosis and treatment of Bright's disease.

TABLE 2—THE ODDS THAT ANY NORMAL PERSON WILL HAVE AS LOW OR A LOWER RATIO THAN THOSE GIVEN IN THE TABLE

Ratio	Odds	
50.4 or less	1 in 2	} Normal
40.5 or less	1 in 15	
39.8 or less	1 in 18	} Doubtful
39.2	1 in 22	
38.5	1 in 28	
37.9	1 in 35	
37.2	1 in 44	
36.5	1 in 56	
35.9	1 in 72	
35.2	1 in 93	
34.5	1 in 122	} Abnormal
33.9 or less	1 in 162	
33.2	1 in 213	
32.6	1 in 286	
31.9	1 in 385	
31.2	1 in 527	
30.6	1 in 741	
27.9	1 in 1,630	

CONCLUSIONS

1 Under certain special conditions, when the amount of secreting tissue in the kidney is constant, the amount of urea excreted in the urine in one hour is directly proportional to the amount of urea in 100 c c of blood sampled during that period.

2 Under certain special conditions, when the amount of secreting tissue in the kidney varies, the ratio $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c c of blood}}$ is directly proportional to the amount of secreting tissue in the kidney.

3 The conditions under which the ratio $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c c of blood}}$ becomes a measure of the amount of secreting tissue in the kidney are, first, that the urea excreting capacity be placed under a strain so that all the secreting tissue is called to full activity, and second, that there be an absence of the effect of certain specific renal stimulants and depressants.

STUDIES IN THE KOTTMANN REACTION FOR THYROID ACTIVITY~

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AND

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The function of the thyroid gland has been studied with, perhaps, greater interest and certainly with more profit by physiologists and clinicians than that of any other gland of internal secretion. During recent years in particular, a remarkable revival of clinical interest has become manifest, stimulated, no doubt, by a number of contributory factors, among which may be mentioned the isolation of thyroxin, the development of a number of simple instruments for the determination of basal metabolism, the study of coagulation alterations associated with thyroid dysfunction, the use of iodids and iodine in public health work, and the development of irradiation in the treatment of hyperthyroidism. It may, therefore, be warranted to present in some detail the study of the Kottmann reaction for thyroid activity, concerning which we have already published a brief note¹

Technic—The technic of the reaction is simple and depends on the protective property of the serum for silver iodid. When the protective power is great, the size of the silver iodid particles dispersed in the serum remains small and the photosensitivity of the silver iodid is reduced. If the protective power of the serum is poor, the silver iodid forms larger particles, becomes more photosensitive, and will, on exposure to light and subsequent development, be readily reduced to metallic silver.

To 1 cc of clear serum, obtained preferably in the morning before meals, 0.25 cc of 0.5 per cent solution of potassium iodid is added and 0.3 cc of a 0.5 per cent solution of silver nitrate. The reagents should be prepared freshly and accurately measured. After mixing by gently agitating the tube, the serum is exposed for five minutes at a distance of 25 cm to a 500 Watt Mazda lamp. Then 0.5 cc of a 0.25 per cent solution of hydroquinone is added, and the color changes noted at definite time intervals. Readings can be made on a 4 plus basis, or colorimetrically against some arbitrary color standard. In some of our work we have used a solution of dialyzed iron for this purpose and readings are then expressed in terms of a color unit. Serum from cases of hyperthyroidism retards the development of the brown color, normal serum turns brown within a short period of time, serum from cases of hypothyroidism accelerates the appearance of the dark brown color.

CLINICAL RESULTS

In our preliminary note we presented the results of 400 tests with this reaction, in which we found that in seventy cases of clinically

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1 Petersen, Dobler, Levinson and Laibe. J. A. M. A. 78:1022 (April 8) 1922.

evident hyperthyroidism sixty-five serums markedly retarded the reaction, two retarded the reaction only slightly, two were normal and one serum accelerated the reaction. In forty-nine cases of simple goiter (colloid and adenomatous) the reaction was in all cases either within normal limits or the serum accelerated the reaction. In 139 serums from normal individuals, three retarded the reaction slightly.

Kottmann² found that the administration of bromids retarded the reaction, just as the addition of bromids directly to the serum retards

TABLE 1—EFFECT OF ADDITION OF POTASSIUM IODID TO SERUM

Patient	Date	Medication	Diagnosis	Goiter	General Condition	Kottmann Reaction
W H K	1/17/22	None	Syphilis	None	Good	+++
	1/19/22	KI (fasting serum)				++
	1/23/22	KI (serum taken after meal)				0
	1/26/22	KI				++

TABLE 2—EFFECT OF FRIGHT ON REACTION

Patient	Date	Diagnosis	Goiter	General Condition	Kottmann Reaction
H D	11/18/21	Minor gunshot wound of face	None	Extreme fright	0
	11/20/21	11/17/21		Nervous	+
A S	12/23/21	Automobile accident	None	Very nervous	0
	12/25/21			Still slightly nervous	+

TABLE 3—EFFECT OF TRAUMA ON SERUM REACTION

Patient	Date	Diagnosis	Goiter	General Condition	Kottmann Reaction
L S	12/22/21	Contusion of brain	None	Drowsy	++
Johnson	11/17/21	Fractured humerus (Accident, 11/16/21)	None	Calm	++
H S	12/23/21	Contusion of brain (Automobile accident, 12/23/21)	None	Unconscious	++
	12/25/21			Unconscious	++
	12/26/21			Semiconscious	++

the reaction. We have studied this effect in a number of patients and have found it quite constant. Merke³ has also confirmed this effect in the serum of epileptics when on bromid medication.

Inasmuch as an excess of iodid added to the serum retards the reaction, we have observed the effect of the administration of iodids in patients. Table 1 illustrates the change in the reaction.

It will be noted that the reaction is retarded, but not, as a rule, so completely as after the ingestion of bromids.

² Kottmann, K. *Schweizer med Wchnschr* **1** 644, 1920

³ Merke, F. *Schweizer med Wchnschr* **51** 200 1921

Fright—We have observed a decided retardation of the reaction with fright, illustrated in Table 2

On the other hand, in patients who had been injured, but were not frightened, or injured and unconscious, the serum reaction was found to be unaltered (Table 3)

The Effect of Thyroidectomy in Exophthalmic Cases—In three cases thyroidectomy was carried out on patients with obvious symptoms of hyperthyroidism and the serum was examined before and after the operation (Table 4)

Effect of Irradiation—We have had the opportunity of studying only one case in which the thyroid region was irradiated. The patient, Mrs T, entered the Augustana Hospital with a history of nervousness. The thyroid gland was slightly enlarged, but there was no evidence of hyperthyroidism and the Kottmann reaction being normal, she was not subjected to operation. She was given one (two-third erythema dose) roentgen-ray treatment over the thyroid and thymic region, and the

TABLE 4—EFFECT OF THYROIDECTOMY ON SERUM REACTION

Patient	Date		General Condition	Kottmann Reaction
H K	11/ 4/21	Before operation		0
	11/18/21	Two weeks after operation	Highly nervous	++
	12/ 2/21		Still nervous	0
	12/ 9/21		Still somewhat nervous	+
Miss B S	11/ 7/21	Before operation	Very nervous	0
	11/18/21		Improved	+++
Mrs A J K	11/26/21	Before operation	Moderate symptoms	0
	1/11/22		Improved	+
	1/14/22		Improved	+++

Kottmann reaction made two weeks later before the patient left the hospital was completely retarded. There were, however, no evidences of hyperthyroidism even at this time.

EXPERIMENTAL DATA

In order to clear up a number of points observed with these clinical cases, we have carried out a series of animal experiments.

The Injection of Thyroxin—We first studied the effect of thyroxin when injected into the blood stream, using dogs for this purpose.

EXPERIMENT 1—Dog 210, weight 9,400 gm, received 5 mg thyroxin intravenously Nov 28, 1921. Serum samples were taken as follows:

Sample		Kottmann Reaction
1	Before injection	++++ (Dark brown)
" 2	30 minutes after injection	++++ (Dark brown)
" 3	1 day after injection	++++ (Dark brown)
" 4	2 days after injection	++++ (Dark brown)
" 5	3 days after injection	++ (Faint brown)
" 6	4 days after injection	— (Unchanged)
" 7	5 days after injection	— (Unchanged)
" 8	7 days after injection	— (Died from distemper)

The fact that the effect of the thyroxin is not immediate, but that a latent period of several days elapses before the effect becomes apparent is illustrated in the second experiment as well as in the first

EXPERIMENT 2—Dog 220, weight 10 kg, injected intravenously with 8 mg thyroxin Dec 12, 1921, at 11 30 a m Serum samples were taken as follows

		Kottmann Reaction
Sample 1	Before injection	++
" 2	3 hours after injection	++++
" 3	1 day after injection	++++
" 4	3 days after injection	++++
" 5	5 days after injection	+
" 6	7 days after injection	—
" 7	9 days after injection	+
" 8	11 days after injection	+
" 9	15 days after injection	+
" 10	18 days after injection	++
" 11	23 days after injection	+++

In this experiment the effect was first observed on the fifth day after injection and was still apparent after two weeks

Thyroidectomy—If injection of thyroxin is followed by a serum alteration made manifest in the Kottmann reaction by a lessening of the sensitivity to light, we might assume that extirpation of the thyroid would result in a hastening of the reaction Kottmann has found this reaction to be accelerated in the serum obtained from myxedema patients

In this group of animals a complete thyroparathyroidectomy was carried out, but in the relatively short period of time that the animals lived, there was no distinct evidence of an alteration of the reaction in the direction expected

EXPERIMENT 3—Dog 225, operated on Dec 15, 1921, both lobes of thyroid removed

		(Colorimeter Readings) Kottmann Reaction
Sample 1	Serum before operation	17
" 2	24 hours after operation	19
" 3	2 days after operation	14
" 4	4 days after operation	12
" 5	6 days after operation	2
" 6	8 days after operation	1 (Distempler)
" 7	12 days after operation	1
" 8	15 days after operation	1
" 9	19 days after operation	15

EXPERIMENT 4—Dog 236, operated on Dec 29, 1921, both lobes of thyroid removed

Sample 1	Serum before operation	20
" 2	During anesthesia	22
" 3	After 24 hours	15
" 4	After 4 days	20

These experiments are, of course, not comparable to the effects that have been recorded by Kottmann with serum from hypothyroid cases In these he found a well defined acceleration of the reaction as con-

trasted with the retardation found in hyperthyroidism It is possible that if the animals were observed for a considerable time some alteration in the serum in the direction expected might be observed

Massage of Thyroid Gland—We next studied the effect of massage of the thyroid gland in dogs with goiters It is, of course, known that the dogs of the Great Lakes region frequently have goiters For our purpose we selected animals having a palpable enlargement

EXPERIMENT 5—Dog 243 Gland massaged Jan 9, 1922

		Kottmann Reaction
Sample 1	Blood taken at 11 45 a m	24
" 2	Masage of thyroid for 1 hour immediately after (12 45)	24
" 3	Three hours after massage (3 45)	125
" 4	24 hours later	10
" 5	72 hours later	Colorless

EXPERIMENT 6—Dog 245, Jan 20, 1922

		Kottmann Reaction
Sample 1	At noon	22
	(Massage for two hours 1 40 to 3 40 p m)	
" 2	At 4 p m	22
" 3	At 8 30 p m	22
" 4	One day later, 1/21/22	22
" 5	Three days later, 1/23/22	10
" 6	Four days later, 1/24/22	00
	(Massage for one hour, 1/25/22)	
" 7	Six days later, 1/26/22	00
	(Massage for one hour, 1/27/22)	
" 8	Eight days later, 1 28/22	00
" 9	Ten days later, 1/30/22	00

EXPERIMENT 7—Dog 246, Jan 24, 1922

Sample 1	At 10 a m	25
	(Massage two hours 10 to 12 noon)	
" 2	At 2 p m	22
" 3	At 6 p m	22
" 4	One day later, 1/25/22	16
	(Massage one hour, 1/27/22)	
" 5	Four days later, 1/28/22	Colorless
" 6	Six days later, 1/30/22	Colorless

The next dog used had no apparent goiter, but the thyroid gland could be palpated The gland was massaged for one hour Jan 27, 1922, and for one hour January 2 After the first massage the tissues of the neck were somewhat edematous and particularly the thyroid lobes were sensitive to touch This continued for several days

EXPERIMENT 8—Dog 256, Jan 27, 1922

		Kottmann Reaction
Sample 1	10 a m, before massage	22
	(10 to 11, massage)	
" 2	At 12 a m	22
" 3	8 a m one day later, 1/28/22	20
" 4	8 a m, three days later, 1/30/22	20
" 5	8 a m six days later, 2/2/22	04
	(Massage one hour)	
" 6	Seven days later, 2/3/22	00

Irradiation—The roentgen ray and other related physical agents have dual effects on tissues,⁴ small doses causing stimulation (functional, formative, etc.) while large doses may cause functional paralysis and destruction of the cells. Like other glandular tissues the thyroid gland is relatively sensitive to irradiation. We might expect, therefore, that small doses would cause some stimulation of the gland and result in an alteration of the Kottmann reaction. We have carried out four experiments in this connection.

EXPERIMENT 9—Dog 178, Oct 29, 1921, irradiation over thyroid area at 8.45 a.m. (Dose 5 minutes, Coolidge tube without filter, 5 inch spark, 10 inch focal distance, 3 ma.)

		Kottmann Reaction
Sample 1	Serum before irradiation	0.0*
" 2	Serum 30 minutes after irradiation	0.9
" 3	1 hour and 30 minutes after irradiation	0.18
" 4	3 hours and 30 minutes after irradiation	0.33

In this experiment, extending over a short period of time, it becomes evident that the first effect of the irradiation is not one indicating hyperthyroidism.

EXPERIMENT 10—Dog 179, Oct 31, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1	Serum before irradiation	1.0
" 2	30 minutes after irradiation	1.5
" 3	1 hour and 30 minutes after irradiation	4.0
" 4	5 hours after irradiation	0.0
" 5	24 hours after irradiation	0.0

EXPERIMENT 11—Dog 180, Nov 1, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1	Serum before irradiation	1.3
" 2	30 minutes after irradiation	2.5
" 3	1 hour and 30 minutes after irradiation	1.1
" 4	6 hours after irradiation	0.7

EXPERIMENT 12—Dog 183, Nov 1, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1	Serum before irradiation	1.0
" 2	30 minutes after irradiation	2.2
" 3	1 hour and 30 minutes after irradiation	2.2
" 4	3 hours and 30 minutes after irradiation	2.2
" 5	7 hours and 30 minutes after irradiation	1.1
" 6	1 day after irradiation	0.5
" 7	3 days after irradiation	0.0
" 8	6 days after irradiation	0.0

All four experiments indicate that the first effect of the irradiation seems to increase the photosensitiveness of the reagents, the color developing more rapidly and to a greater depth in the serum samples taken during the hours immediately following the irradiation. After this time, however, the reaction is reversed and the serum reaction is retarded. In no case is the reaction retarded to the extent that one finds in serum from cases of hyperthyroidism.

*The reaction delayed, an experience met with not infrequently in dogs.
4 Petersen and Saellhof. *Am J M Sc* **163** 391 (March) 1922.

In the next dog the dose was increased (10 minutes) and the serum examined for a longer time after the irradiation

EXPERIMENT 13—Dog 209, Nov 28, 1921 Irradiation at 11 30 a m

			Kottmann Reaction
Sample 1	Blood before irradiation		20
" 2	1 hour after irradiation		20
" 3	1 day after irradiation		15
" 4	2 days after irradiation		175
" 5	3 days after irradiation		175
" 6	4 days after irradiation		175
" 7	5 days after irradiation		175
" 8	7 days after irradiation		05
" 9	9 days after irradiation		00
" 10	12 days after irradiation		00 Killed

It will be observed that in this case the evidence of increase in the thyroid activity was not apparent until about seven days after the irradiation, if we exclude the transient alteration that was apparent twenty-four hours after the raying

Irradiation of Other Regions Liver—During the course of the work it seemed probable that any cellular destruction that would entail the accumulation of the products of tissue destruction in the blood stream might influence the Kottmann reaction With a large dose of roentgen-rays we might anticipate the presence of such fragments derived from the cellular destruction of the liver parenchyma An experiment was made to determine the point

EXPERIMENT 14—Dog 234, Dec 12, 1921 Liver area rayed for a total of forty-five minutes, no filter, 5 inch spark gap, 3 ma, 10 inch focal distance

			Kottmann Reaction
Sample 1	Before irradiation		20
" 2	1 hour after irradiation		20
" 3	4 hours after irradiation		15
" 4	1 day after irradiation		14
" 5	3 days after irradiation		10
" 6	6 days after irradiation		10
" 7	9 days after irradiation		15

Here again the reaction observed is not of the type seen with exophthalmic serums, because the delay in the serum reaction is transient, after 5 minutes the color in the tubes is usually equalized

Chloroform Necrosis of the Liver—That the reaction is delayed when the liver is injured by other methods was observed when we produced a chloroform necrosis of the liver in dogs (two days starvation, one hour chloroform anesthesia) The serum from these animals examined two days after the anesthesia was bile stained and the Kottmann reaction was considerably retarded

The experiments make probable the assumption that any extensive tissue injury may bring about serum alterations similar in character to those produced in hyperthyroidism It is, of course, not excluded that irradiation of this kind and other related injuries may mobilize sub-

stances which, on entering the blood stream, may stimulate the thyroid gland. We are of the impression that the first explanation is the correct one.

Effect of Bacterial Intoxication—In order to determine the effect of a severe intoxication (produced by the injection of colon bacilli) the following experiment was carried out.

EXPERIMENT 15—Dog 233, Dec 21, 1921, weight, 13.2 kg, injected intravenously with 500 mg (moist weight) of a fresh culture of colon bacilli, at 10:30 a. m.

		Kottmann Reaction
Sample 1	Before injection	1.25
" 2	30 minutes after injection	0.7
" 3	1 hour and 30 minutes after injection	0.0
" 4	3 hours and 30 minutes after injection	0.62

Effect of Peptone Injection—

EXPERIMENT 16—Dog 231, weight, 7.5 kg, injected with 2 gm Witte peptone intravenously at 10:35 a. m.

		Kottmann Reaction
Sample 1	Before injection	1.9
" 2	10 minutes after injection	
Serum flocculates when hydrocholin is added		
" 3	1 hour after injection	1.3
" 4	4 hours after injection	1.6

The animal was in shock for about thirty minutes after the injection, but made a complete recovery within an hour. The reaction was somewhat delayed.

Effect of Peptone Ingestion—

EXPERIMENT 17—Dog 237, weight, 8 kg, given 50 gm Armour's peptone by mouth at 10 a. m.

		Kottmann Reaction	Leukocyte Count
Sample 1	Before injection	2.0	12,000
" 2	30 minutes later	2.0	14,300
" 3	1 hour and 30 minutes later	1.7	40,000
" 4	4 hours later	1.8	28,400
" 5	24 hours later	1.9	14,000

While the animal reacted with a distinct leukocytosis, the Kottmann reaction was not altered to any marked extent, only a slight retardation being apparent.

Effect of Trypsin Ingestion—

EXPERIMENT 18—Dog 182, 15 gm trypsin (in the form of enteric pills) was placed directly into the small intestines through a small enterostomy opening.

The effect on the serum was studied at the following intervals.

		Kottmann Reaction
Sample 1	Before administration of trypsin	1.1
" 2	2 hours after	1.4
" 3	4 hours after	1.1
" 4	6 hours after	0.4
" 5	10 hours after	1.0
" 6	24 hours after	1.4

In another experiment trypsin in solution was injected directly into the small intestine in the same dog at 11 30 a m (20 gm)

EXPERIMENT 19—Dog 182 The serum was studied at the following intervals
Kottmann Reaction

Sample 1	Before injection	11
" 2	1 hour later	11
" 3	2 hours later	04
" 4	4 hours later	09
" 5	8 hours later	06
" 6	24 hours later	12

Effect of Hemorrhage on the Kottmann Reaction —

EXPERIMENT 20—Dog 184, weight, 7 kg Bled as follows

		Kottmann Serum
Sample 1	100 c c	20
" 2	100 c c 1 hour later	16
" 3	100 c c 2 hours later	16
" 4	60 c c 3 hours later	14
" 5	80 c c 4 hours later	10

EXPERIMENT 21—Dog 199, 9,600 gm Bled as follows

		Kottmann Serum	Plasma
Sample 1	300 c c	125	125
" 2	80 c c 1 hour later	15	085
" 3	80 c c 2 hours later	125	05
" 4	80 c c 3 hours later	07	00

EXPERIMENT 22—Dog 200, 8,100 gm Bled as follows

		Kottmann Serum
Sample 1	100 c c	17
" 2	100 c c 1 hour later	17
" 3	100 c c 2 hours later	14
" 4	100 c c 3 hours later	05

EXPERIMENT 23—Dog 238, the reaction was not altered

EXPERIMENT 24—Dog 265, 21,000 gm, bled as follows

		Kottmann Serum
Sample 1	500 c c 10 a m	15
" 2	50 c c 10 30 a m	15
" 3	50 c c 11 a m	20
" 4	50 c c 1 p m	20
" 5	50 c c 4 p m	15
" 6	50 c c 11 a m following day	10

Exercise—The effect of exercise on the Kottmann reaction was studied. An electrically driven treadmill was used in which the dogs were placed for two hour runs. The serum showed no alteration with exercise of this degree.

When the duration of the experiment was prolonged, some effect was observed, as is shown in the following experiment

EXPERIMENT 25—Dog 235, Dec 23, 1921

		Kottmann Serum
Sample 1	Before (Treadmill six hours, about 90,000 feet)	20
" 2	Immediately after exercise	175
" 3	Following morning	10

While the effect seemed apparent in the direction of retardation, this was never marked and could by no means be compared to the retardation obtained with exophthalmic serums

DISCUSSION

Inasmuch as we were able to confirm the clinical usefulness¹ of the Kottmann reaction in making apparent certain alterations in thyroid activity associated with hyperthyroidism, we have in these experiments sought to determine whether the reaction indicated the presence of the thyroid secretion in the blood, or whether the active substance of the gland brought about alterations in the tissue metabolism, which then became manifest in an indirect way in the Kottmann reaction

Our experiments support this latter contention. Apart from the fact that when thyroxin is directly added to serum, the Kottmann reaction is not retarded, we found that injection into animals was not followed by an immediate change in the reaction, but that a period of several days elapsed (from three to five) before the effect of the injection became apparent in the serum. This corresponds with the clinical experience that with injection of thyroxin the maximum effect does not become apparent for a number of days, but then may persist for ten days or more. This corresponds with the effect on the Kottmann reaction observed in dogs.

We have, furthermore, been able to demonstrate that following irradiation of the thyroid region with moderate doses of roentgen rays a similar effect may be brought about. This observation, too, coincides with the frequent clinical observation of thyroid activation during the course of roentgen-ray irradiation of the gland as a therapeutic measure.

Massage of the hypertrophied gland in dogs also results in a retardation of the serum reaction three or four days after the massage. In the single experiment with massage of a normal gland some retardation was also observed, but not to the same extent as with the goiter dogs.

Other experiments which were made (massive roentgen-ray irradiation of the liver, peptone shock, bacterial shock, hemorrhage, etc.) were all followed by definite serum alteration, usually in the direction of a retardation of the reaction. This we believe is in these cases brought about by an alteration in the globulin ratio of the serum, as well as alterations in the hydrogen ion balance, a subject which will be taken up in a subsequent paper.

It is evident from the results of these experiments that the alterations in the reaction with serum obtained under different experimental conditions need not be associated with thyroid dysfunction. The thyroid dysfunction alters cellular metabolism and this, in turn, alters the physical properties of the serum so that in cases of hyperthyroidism the serum is a better protective agent than normally. If the cellular

metabolism is altered by other insults, serum alterations must also take place and these will be reflected in the Kottmann reaction. It is needless to emphasize that for general clinical work great weight need not be attached to changes other than those involved in thyroid dysfunction, because we have not found that they alter the reaction (in dogs) to a degree comparable with the alterations produced in thyroid disturbances in clinical material.

We have observed that dog serum when standing for several days in the refrigerator loses its protective power to a considerable extent, differing in this from serums obtained from cases of hyperthyroidism, which have been kept for several weeks with only a partial loss of their protective property. Comparative tests made with dog serum must therefore always be made on fresh serum under strictly uniform conditions.

CONCLUSIONS

1 In clinical cases of hyperthyroidism the Kottmann reaction may return to normal after thyroidectomy. Fright, on the other hand, produced a positive reaction in two patients, in control patients who were subjected to similar trauma, but who were not frightened (one unconscious, one semiconscious, the other conscious and calm) the reaction was within normal limits.

2 Experimentally it has been found that thyroxin injections, irradiation and massage of the hypertrophied gland resulted in an increased protective property of the serum which became manifested in the course of several days. The serum alteration is, therefore, not a direct one, but is evidently the result of alterations in cellular metabolism brought about by the increased thyroid activity.

3 Other experimental procedures may alter the reaction (bacterial shock, peptone shock, trypsin ingestion, hemorrhage, irradiation of remote organs). In no case was the delay in the reaction comparable to that observed with exophthalmic serums and we do not believe that the alterations in the reactions observed under these experimental conditions will detract from the clinical usefulness of the test in the diagnosis and the control of the therapy of thyroid dysfunction.

THE GLUCOSE MOBILIZATION RATE IN HYPERTHYROIDISM

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In a preliminary paper ¹ on this subject the results of some observations on the glucose mobilization rate in hyperthyroidism were reported. In this paper the results will be exhibited in greater detail. Ten normal controls and ten well marked cases of exophthalmic goiter have been studied under identical conditions. All the cases of hyperthyroidism were of the same type, i e, exophthalmic goiter, with all the clinical manifestations of a well marked thyrotoxicosis.

The object of the experiments was to obtain some insight into the mechanism of so-called decreased carbohydrate tolerance in cases of hyperthyroidism. Through studies of the change in the blood sugar, the respiratory quotient and the total metabolism, before and after glucose ingestion, we derived our data for computing the carbohydrate utilization.

The procedure need not be gone over again in detail as it was clearly outlined in the preliminary paper. A Tissot spirometer, equipped with a Siebe-Gorman half face mask and Douglas valves, and a Haldane gas analysis apparatus, were used routinely in all the experiments under the standard technic for this type of work. Samples of the total expired air were taken over mercury in a special sampling tube for analysis. All technical results and calculations were carefully checked over, and all sources of error eliminated, in so far as it was possible. Altogether the experiment occupied about three and one-half hours. The fasting patient was put to rest for from one-half to three-quarters of an hour after which a basal period was run. The mask was then replaced for a second basal period. The basal respiratory quotient and total metabolism used in our calculations were the average of these two periods. As soon as these were completed, blood was taken for a fasting blood sugar, and the glucose was given in a mixture of grapefruit juice—for the most part the dosage was 1.75 gm per kilogram body weight ². In one or two of the first experiments 100 gm was given without regard to weight. Fifteen minutes after the ingestion of the glucose, the blood sugar was taken, and five minutes later (i e, twenty minutes after glucose ingestion), the mask was replaced for

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1 Sanger, B J. Proc Soc Exper Biol & M **17** 117, 1921.

2 Janney and Isaacson. J A M A **70** 1131 (April 20) 1918.

the first postglucose period. The duration of the periods was usually ten minutes. This made the first period end on the half hour after the taking of the glucose. From then on until the end of the experiment a period was run every half hour, making in all five postglucose periods. Blood was withdrawn again one hour and two hours after the glucose ingestion. This gave us two basal periods and five postglucose periods, and four samples of blood for analysis. A specimen of urine taken at the end of the experiment was tested for glucose. With the data obtained, the calculations were made and tabulated.

The comparison of the change in the metabolic rate between the normals and the cases of hyperthyroidism was very confusing. The percentage rise above basal was much less in the cases of exophthalmic goiter than in the controls, but if the abnormal cases were figured on the basis of what the rise in calories would have amounted to had the patient's basal metabolism been normal, then the results were very

TABLE 1—BLOOD SUGAR CURVES IN NORMAL CONTROLS

	Name										Average
	C L	H D	W V G	F H	B S	M C	M C	H J	R Mc	H R G	
Fasting	0.89	0.83	0.91	0.90	0.80	0.87	0.72	1.10	0.92	Lost	0.85
15 minutes	0.98	1.05	1.19	1.37	1.09	1.10	1.24	1.20	1.03	0.76	
60 minutes	1.20	1.08	0.93	1.51	1.35	1.26	1.54	1.67	1.40	0.78	
120 minutes	0.95	0.95	1.10	1.14	1.15	1.17	1.20	1.20	1.03	0.73	
Range	0.41	0.25	0.28	0.59	0.55	0.39	0.82	0.57	0.48		0.48

TABLE 2—BLOOD SUGAR CURVES IN CASES OF HYPERTHYROIDISM

	Name										Average
	F B	H G	F k	O E	L M	A S	M D	G S	B S	F R	
Fasting	0.91	0.95	1.02	1.03	0.93	1.13	0.91	1.00	1.12	0.94	0.99
15 minutes	1.3	1.25	1.54	1.40	1.37	2.00	1.50	1.40	1.74	1.30	
60 minutes	2.10	2.30	2.32	2.04	1.80	2.32	1.90	1.80	2.10	1.50	
120 minutes	1.85	2.30	2.00	1.50	1.30	1.07	1.66	1.04	1.40	1.07	
Range	0.94	1.35	1.30	1.01	0.87	1.19	0.99	0.80	0.98	0.56	1.00

similar to those obtained in the normal controls. It seems likely, therefore, that the specific dynamic action of carbohydrates is much the same in cases of hyperthyroidism and in normal persons.

Taking as a normal blood sugar curve, one that has a fasting level from 0.7 to 1.1 gm per liter, that reaches its peak in one hour after glucose ingestion, rarely going higher than 1.7, and which tends to reach its fasting level within two hours, then our ten normal controls were well within this range (Table 1).

In no case did glucose appear in the urine.

The cases of hyperthyroidism showed essentially normal fasting blood sugars, though on the average they were somewhat higher than the fasting values found in the normals (Table 2). The range in the great majority of cases studied, however, was quite different. There

was a distinct rise after fifteen minutes, but the peak was not reached until after one hour when it was distinctly above the normal range. The blood sugar, in the great majority of cases, remained distinctly elevated after two hours. There was one notable exception to this in one case (E R, a very distinct case of exophthalmic goiter), in which the blood sugar curve was entirely normal. At the time of the test this patient had auricular fibrillation which was almost certainly secondary to the thyrotoxicosis, as it cleared up entirely (electrocardiograph evidence) under treatment. This rather strikingly normal curve in a well marked case, along with one or two other cases in the series that were within normal variation, showed that all cases of hyperthyroidism do not have deranged carbohydrate metabolism if judged by blood sugar curves alone. Five of the cases showed glycosuria after the glucose ingestion, three were sugar free and two were not tested through error.

TABLE 3—CURVES OF RESPIRATORY QUOTIENT IN NORMAL CONTROLS

	Name										Average
	C L	H D	W V G	E H	B S	M C	M C	H J	R Mc	H R G	
Basal	0.78	0.83	0.75	0.77	0.78	0.79	0.83	0.85	0.83	0.75	0.80
30 minutes	0.82	0.81	0.84	0.80	0.80	0.82	0.83	0.83	0.88	0.79	
60 minutes	0.80	0.80	0.88	0.80	0.84	0.88	0.86	0.84	0.84	0.81	
90 minutes	0.89	0.88	0.88	0.90	0.86	0.89	0.83	0.88	0.88	0.80	
120 minutes	0.87	0.88	0.84	0.92	0.88	0.92	0.92	0.93	0.93	0.83	
150 minutes	0.94	0.90	0.90	0.90	0.86	0.93	0.90	0.89	0.92	0.87	0.12
Range	0.16	0.09	0.15	0.15	0.10	0.14	0.09	0.10	0.10	0.12	

TABLE 4—CURVES OF RESPIRATORY QUOTIENT IN CASES OF HYPERTHYROIDISM

	Name										Average
	F B	H G	F K	C L	L M	A S	M D	G S	B S	J R	
Basal	0.75	0.76	0.76	0.75	0.75	0.74	0.79	0.79	0.81	0.72	0.76
30 minutes	0.81	0.79	0.81	0.84	0.88	0.83	0.82	0.79	0.88	0.76	
60 minutes	0.90	0.86	0.90	0.92	0.98	0.84	0.97	0.91	0.92	0.83	
90 minutes	0.91	0.91	0.92	1.00	0.97	0.88	0.97	1.00	0.97	0.85	
120 minutes	0.91	0.90	0.91	1.03	0.96	0.85	0.98	0.98	0.97	0.92	
150 minutes	0.99	0.92	0.94	1.05	0.95	0.80	0.97	0.96	0.96	0.89	0.20
Range	0.21	0.16	0.18	0.30	0.23	0.15	0.19	0.21	0.16	0.20	

The respiratory quotients when studied in phases offered the most interesting data in our experiments. The basal quotient on the average in the cases of hyperthyroidism was slightly lower than in the normal controls—0.76 as compared to 0.80 (Tables 3 and 4). In the cases of exophthalmic goiter after the dose of glucose had been given, the quotients rose rapidly to a high figure, in one case going as high as 1.05, whereas in the normal cases, the quotients rose more slowly, and did not reach nearly so high a point. The high level of the respiratory quotient was maintained for a longer time in the cases of hyperthyroidism than in the normal controls, and at the end of the two and one-half hours was still very high. The average range from the basal to the peak in the cases of hyperthyroidism was twenty points,

while that in the normals was only twelve, the greatest being thirty in the one and sixteen in the other. This proves very strikingly that individuals with thyrotoxicosis can burn carbohydrate readily, in fact, do burn it with avidity, and along with the fact that their blood sugar stays high suggests very probably that there is an inability for storing carbohydrate in these cases. For if they burn it more rapidly than do normals, and in spite of this maintain a high blood sugar, then obviously they cannot be storing it. There is good experimental evidence to substantiate this view.³

From the figures of the respiratory quotient we derived our calculations for the utilization of carbohydrate. Fifteen per cent was deducted from the total calories per hour for that portion of the heat derived from protein metabolism.⁴ The remaining calories were assumed as coming from carbohydrate and fat, and were apportioned to each of these metabolites according to the percentage tables of Zunst and Schumburg as modified by Riche and Lusk. The respiratory quotients were used directly without deductions for protein metabolism as derived from the urinary nitrogen, that is, they were not nonprotein respiratory quotients. For practical purposes of comparison this seemed adequate, though we realized that nitrogen studies would have made our data somewhat more accurate. The difficulty of collecting specimens over short periods, however, and the uncertainty of the nitrogen in the urine collected representing the protein utilized during the period of the experiment, due to the nitrogen lag, decided us to leave urinary studies out of our work. Tables 5 and 6 show the calculations in each case.

It is evident that in the normal cases following the dose of glucose, there was an increase in the number of grams of carbohydrate utilized over the amount utilized at basal. This increase, however, was only a small proportion of the quantity ingested, the total for the two and one-half hours following the ingestion of the dose being on the average 18.1 per cent of the amount taken (Table 7). This, plus the rapid rise and fall in the blood sugar, makes us feel that in these cases the greater part of the carbohydrate is stored.

In the cases of hyperthyroidism, on the other hand, an average of 36.1 per cent (Table 8) of the amount ingested was burned over the same period (two and one-half hours) and at the end of this period the blood sugar was still greatly elevated. The amount of carbohydrate accounted for by this increased blood sugar is very small, only amounting to a few grams, but when we realize that the maintained high concentration of sugar in the blood means a high concentration of sugar in the tissues, this figure is more significant.

³ Cramer and Krause. *Proc. Roy. Soc., Ser. B* **86** 50, 1913. Kurivama. *J. Biol. Chem.* **33** 193, 1918.

⁴ Voit. *E. Ztschr. f. Biol.* **41** 188, 1901.

TABLE 5—DATA ON TEN NORMAL CONTROLS AFTER GLUCOSE INGESTION

	Respiratory Quotient	Calories per Hr	Rise, Calories per Hr	Calories per Sq M per Hr	Per Cent Rise Above Basal	Per Cent Rise Above Normal	Calories from Carbohydrate and Fat*	Per Cent Calories from Carbohydrate	Calories from Carbohydrate	Gm Carbohydrate Utilized Total increase	Blood Sugar, Gm per Liter
C. L., ♂, 26 Ht., 176.9 Cm Wt., 65 Kg Dose of glucose, 114 Gm											
Basal	0.8	65.5	0	36.4	0	0	55.7	25.2	11.0	3.4	0.89
Post glucose											
30 minutes	0.82	72.8	8.3	41.0	13	12	62.7	38.8	24.3	5.9	0.95†
60 minutes	0.80	73.2	7.7	40.6	12	11	62.2	32.0	19.9	1.9	1.3
90 minutes	0.89	70.7	5.2	39.3	8	7	60.2	62.6	37.7	9.2	0.95
120 minutes	0.87	66.3	0.8	36.9	1	0	56.4	57.8	31.1	7.7	0.95
150 minutes	0.91	68.9	3.1	38.3	5	5	58.6	79.6	46.6	11.4	0.95
H. D., ♂, 26 Ht., 175.2 Cm Wt., 68 Kg Dose of glucose, 120 Gm											
Basal	0.83	67.1	0	36.7	0	0	57.4	42.2	24.2	5.9	0.88
Post glucose											
30 minutes	0.81	74.6	7.5	40.8	11	10	63.4	35.1	22.1	5.1	1.05†
60 minutes	0.80	71.7	4.6	39.2	6	6	60.9	32.0	19.5	1.8	1.08
90 minutes	0.88	67.5	7.9	41.0	11	11	63.8	59.2	37.8	9.2	0.95
120 minutes	0.88	79.8	12.7	43.6	18	17	67.8	59.2	10.1	9.8	0.95
150 minutes	0.90	77.3	10.2	42.2	14	14	65.7	66.0	43.4	10.6	0.95
W. V. G., 32 Ht., 185.6 Cm Wt., 71.9 Kg Dose of glucose, 126 Gm											
Basal	0.75	77.3	0	39.8	0	0	65.7	15.0	9.9	2.4	0.91
Post glucose											
30 minutes	0.84	84.7	7.4	43.7	10	10	72.0	45.6	32.8	5.0	1.19†
60 minutes	0.88	86.3	9.0	44.5	12	12	73.4	59.2	13.4	10.6	0.93
90 minutes	0.88	89.7	12.4	46.2	16	17	76.2	59.2	15.1	11.0	0.93
120 minutes	0.81	89.7	12.4	46.3	16	17	76.2	45.6	31.7	8.5	1.1
150 minutes	0.90	82.5	5.2	42.5	7	8	70.1	66.0	16.3	11.3	0.93
F. H., ♀, 23 Ht., 171.1 Cm Wt., 52 Kg Dose of glucose, 91 Gm											
Basal	0.77	55.1	0	34.4	0	0	46.8	21.8	10.2	2.5	0.92
Post glucose											
30 minutes	0.80	59.8	1.7	37.4	9	8	50.8	32.0	16.3	4.0	1.37†
60 minutes	0.80	60.8	5.7	38.0	10	10	51.7	32.0	16.6	4.0	1.51
90 minutes	0.90	63.4	8.3	39.6	15	14	53.9	66.0	35.6	8.7	0.92
120 minutes	0.92	65.4	10.3	40.9	19	18	55.6	72.8	40.5	9.9	1.11
150 minutes	0.90	63.1	8.0	39.5	15	14	53.6	66.0	35.4	8.6	0.92
B. S., 29 Ht., 169 Cm Wt., 51.6 Kg Dose of glucose, 90 Gm											
Basal	0.78	51.8	0	32.8	0	0	44.0	25.2	11.1	2.7	0.8
Post glucose											
30 minutes	0.80	56.9	5.1	36.0	10	8	48.4	32.0	15.5	3.8	1.09†
60 minutes	0.84	59.0	7.2	37.3	14	11.4	56.2	45.6	22.9	5.6	1.35
90 minutes	0.86	57.8	6.0	36.6	12	9.6	49.1	52.1	25.7	6.3	0.95
120 minutes	0.88	60.4	8.6	38.2	16	13.7	51.3	59.2	20.4	7.4	1.15
150 minutes	0.86	59.1	4.3	35.5	8	6.8	47.7	52.1	25.0	6.1	0.95
M. C., ♀, 25 Ht., 154.4 Cm Wt., 51 Kg Dose of glucose, 89 Gm											
Basal	0.79	52.9	0	36.0	0	0	45.0	28.6	12.9	3.1	0.87
Post glucose											
30 minutes	0.82	55.2	2.3	37.6	4	4	46.9	38.8	18.2	4.4	1.1†
60 minutes	0.88	53.6	0.7	36.5	1	1	45.6	59.2	27.0	6.6	1.26
90 minutes	0.89	55.3	2.4	37.6	4	4	47.0	62.6	29.4	7.2	0.95
120 minutes	0.92	53.7	0.8	36.5	1	1	45.6	72.8	33.2	8.1	1.17
150 minutes	0.93	54.5	1.6	37.1	3	3	46.3	76.2	35.3	8.6	0.95

* 15 per cent deducted from calories per hour for calories from (nitrogen) protein

† Blood sugar 15 minutes post glucose

TABLE 5—DATA ON TEN NORMAL CONTROLS
AFTER GLUCOSE INGESTION—(Continued)

	Respiratory Quotient	Calories per Hr	Rise, Calories per Hr	Calories per Sq M per Hr	Per Cent Rise Above Basal	Per Cent Rise Above Normal	Calories from Carbohydrate and Fat*	Per Cent Calories from Carbohydrate	Calories from Carbohydrate	Gm Carbohydrate Utilized		Blood Sugar, Gm per Liter
										Total	Increase	
M. C., ♂, 25 Ht., 171.6 Cm Wt., 53.5 Kg Dose of glucose, 95 Gm												
Basal	0.83	62.0	0	38.0	0	0	52.7	42.2	22.2	5.4		0.72
Post glucose												
30 minutes	0.83	64.8	2.8	39.7	4	4	55.1	42.2	23.3	5.7	0.3	1.24†
60 minutes	0.86	64.4	2.4	39.5	4	4	54.7	52.4	28.7	7.0	1.6	1.54
90 minutes	0.83	65.1	3.1	39.9	5	5	55.3	42.2	23.3	5.7	0.3	
120 minutes	0.92	65.5	3.5	40.2	6	6	55.7	72.8	40.6	9.9	4.5	1.2
150 minutes	0.90	65.2	3.2	40.0	5	5	55.4	66.0	36.6	8.9	3.5	
H. J., 22 Ht., 170.9 Cm Wt., 63 Kg Dose of glucose, 110 Gm												
Basal	0.85	66.9	0	38.4	0	0	56.9	49.0	27.8	6.77		1.1
Post glucose												
30 minutes	0.83	72.7	5.8	41.8	9	8.6	61.8	42.2	26.1	6.37	-0.4	1.2†
60 minutes	0.84	73.6	6.7	42.3	10	9.8	62.6	45.6	28.6	6.97	0.2	1.67
90 minutes	0.88	71.7	4.8	41.2	7	7	60.9	59.2	36.0	8.8	2.03	
120 minutes	0.93	73.7	6.8	42.3	10	9.8	62.6	76.2	47.7	11.6	4.8	1.2
150 minutes	0.89	71.5	4.6	41.1	7	7	60.8	62.6	38.1	9.3	2.5	
R. Mc., 22 Ht., 181.5 Cm Wt., 78.5 Kg Dose of glucose, 137 Gm												
Basal	0.83	66.7	0	33.5	0	0	56.7	42.2	23.9	5.8		0.92
Post glucose												
30 minutes	0.88	74.3	7.6	37.3	11	10	63.2	59.2	37.4	9.1	3.3	1.03†
60 minutes	0.84	76.9	10.2	38.6	15	13	65.4	45.6	29.8	7.3	1.5	1.4
90 minutes	0.89	78.2	11.5	39.9	17	15	66.5	61.0	40.5	9.9	4.1	
120 minutes	0.93	75.3	8.6	37.8	13	11	64.0	76.2	48.7	11.9	6.1	1.03
150 minutes	0.92	77.9	11.2	39.1	17	14	66.2	72.8	48.2	11.8	6.0	
H. R. G., ♂, 36 Ht., 172 Cm Wt., 70.7 Kg Dose of glucose, 100 Gm												
Basal	0.75	65.3	0	35.5	0	0	55.5	15.0	8.3	2.0		Lost
Post glucose												
30 minutes	0.79	69.3	4.0	37.7	6	6	58.9	28.6	16.8	4.1	2.1	0.76†
60 minutes	0.81	69.3	4.0	37.6	6	6	58.9	35.4	20.8	5.1	3.1	0.78
90 minutes	0.86	73.6	8.3	40.0	12	11	62.6	52.4	32.8	8.0	6.0	
120 minutes	0.83	70.8	5.5	38.5	8	8	60.2	42.2	25.4	6.2	4.2	0.73
150 minutes	0.87	72.8	7.5	39.5	11	10	61.9	55.8	34.6	8.4	6.4	

* 15 per cent deducted from calories per hour for calories from (nitrogen) protein

† Blood sugar 15 minutes post glucose

The explanation seems obvious. In cases of hyperthyroidism there is a deficiency in the ability to store carbohydrate. This makes for a carbohydrate plethora and the carbohydrate plethora stimulates carbohydrate metabolism. This inability to store carbohydrate appears to be the only logical explanation of the carbohydrate plethora, as it cannot be due to the inability of the tissues to utilize it in this condition. Besides, this explanation fits in with the experimental evidence, as Cramer and his collaborators and Kuriyama have shown that thyroid

TABLE 6—DATA ON TEN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE WAS ADMINISTERED

	Respiratory Quotient	Calories per Hr	Rise, Calories per Hr	Calories per Sq M per Hr	Per Cent Rise Above Basal	Per Cent Rise Above Normal	Calories from Carbohydrate and Fat*	Per Cent Calories from Carbohydrate	Calories from Carbohydrate	Gm Carbohydrate Utilized		Blood Sugar, Gm per Liter
										Total	Increase	
F B, 32 Ht, 174 Cm Wt, 53.8 Kg Dose of glucose, 91.1 Gm												
Basal	0.75	95.0	0	58.0	0	0	80.8	15.0	12.1	3.0		0.91
Post glucose												
30 minutes	0.81	101.3	9.3	63.6	9	14	88.6	15.6	40.5	9.9	6.9	1.3†
60 minutes	0.90	101.3	9.3	63.6	9	11	88.6	66.0	58.5	11.2	11.2	2.1
90 minutes	0.91	106.2	11.2	64.7	11	18	90.3	69.1	62.5	15.2	12.2	
120 minutes	0.91	105.3	10.3	61.2	10	17	89.5	79.6	71.1	17.1	11.4	1.85
150 minutes	0.99	103.2	8.2	62.0	8	13	87.7	96.6	81.9	20.6	17.6	
H G, 22 Ht, 160.5 Cm Wt, 47.8 Kg Dose of glucose, 81 Gm												
Basal	0.76	85.9	0	58.0	0	0	73.0	18.1	13.1	3.3		0.95
Post glucose												
30 minutes	0.79	93.1	7.5	63.1	9	13	79.4	28.6	22.7	5.5	2.2	1.25†
60 minutes	0.86	89.6	3.7	60.5	4	6	76.2	52.4	39.9	9.7	6.4	2.3
90 minutes	0.91	89.7	3.8	60.6	4	6	76.3	69.4	53.0	12.9	9.6	
120 minutes	0.90	90.1	1.2	60.9	5	7	76.6	66.0	56.6	12.3	9.0	2.3
150 minutes	0.92	90.1	1.2	60.9	5	7	76.6	72.8	55.8	13.6	10.3	
F K, 24 Ht, 145 Cm Wt, 37 Kg Dose of glucose, 65 Gm												
Basal	0.76	68.7	0	56.0	0	0	58.4	18.4	10.7	2.6		1.02
Post glucose												
30 minutes	0.81	67.5	-1.2	51.9	-2	-3	57.4	35.4	20.6	5.0	2.4	1.51†
60 minutes	0.90	71.1	2.4	57.8	3	5	60.4	60.0	39.9	9.7	7.1	2.32
90 minutes	0.92	64.9	-3.8	52.8	-6	-9	55.1	72.8	40.1	9.8	7.2	
120 minutes	0.91	67.3	-1.1	54.7	-2	-3	57.2	79.6	45.5	11.1	8.5	2.0
150 minutes	0.91	59.2	-9.5	48.1	-14	-21	50.3	79.6	40.0	9.8	7.2	
C E, 30 Ht, 169 Cm Wt, 52.5 Kg Dose of glucose, 92 Gm												
Basal	0.75	80.2	0	50.5	0	0	68.2	15.0	10.2	2.5		1.03
Post glucose												
30 minutes	0.84	89.3	9.1	56.1	11	15	75.9	45.6	31.6	8.4	5.0	1.1†
60 minutes	0.925	80.5	0.3	50.6	0	0	68.1	71.0	50.6	12.3	9.8	2.01
90 minutes	1.00	87.9	7.7	55.3	0	13	74.7	100.0	74.7	18.2	15.7	
120 minutes	1.03	91.2	11.0	57.4	14	19	77.5	100.0	77.5	18.9	16.1	1.5
150 minutes	1.05	87.5	7.3	55.1	9	12	71.5	100.0	74.5	18.2	15.7	
I. M., 44 Ht, 153 Cm Wt, 46.6 Kg Dose of glucose, 82 Gm												
Basal	0.75	78.7	0	55.8	0	0	66.9	15.0	10.0	2.1		0.93
Post glucose												
30 minutes	0.88	90.3	11.6	61.0	15	23	76.8	59.2	45.5	11.1	8.7	1.37†
60 minutes	0.98	89.1	10.7	63.4	14	21	76.0	93.2	70.8	17.3	14.9	1.8
90 minutes	0.97	86.2	7.5	61.1	10	15	73.3	89.8	65.8	16.0	13.6	
120 minutes	0.96	82.2	3.5	58.3	4	7	69.9	86.4	60.4	14.7	12.3	1.3
150 minutes	0.95	79.5	0.8	56.1	1	2	67.6	83.0	56.1	13.7	11.3	
A S., 43 Ht, 169.5 Cm Wt, 41 Kg Dose of glucose, 72 Gm												
Basal	0.74	86.0	0	60.8	0	0	73.9	11.6	8.6	2.1		1.13
Post glucose												
30 minutes	0.83	95.0	8.1	66.5	9	16	80.8	42.2	34.1	8.3	6.2	2.0†
60 minutes	0.81	91.7	4.8	61.1	5	9	78.0	45.6	35.6	8.7	6.6	2.32
90 minutes	0.88	90.1	3.2	63.0	1	6	76.6	59.2	45.3	11.0	8.9	
120 minutes	0.85	87.6	0.7	61.3	1	1	74.5	49.0	36.5	8.0	6.8	1.07
150 minutes	0.89	81.7	-2.2	59.2	-2	-4	72.0	62.6	45.1	11.0	8.9	

* 15 per cent deducted from calories per hour for calories from (nitrogen) protein
† Blood sugar 15 minutes post glucose

TABLE 6—DATA ON TEN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE WAS ADMINISTERED—(Continued)

	Respiratory Quotient	Calories per Hr	Rise, Calories per Hr	Calories per Sq M per Hr	Per Cent Rise Above Basal	Per Cent Rise Above Normal	Calories from Carbohydrate and Fat*	Per Cent Calories from Carbohydrate	Calories from Carbohydrate	Gm Carbohydrate Utilized		Blood Sugar, Gm per Liter
										Total	Increase	
M D 30 Ht, 164.5 Cm Wt, 57.3 kg Dose of glucose, 100 Gm												
Basal	0.79	87.1	0	53.8	0	0	74.1	28.6	21.1	5.1		0.91
Post glucose												
30 minutes	0.82	89.8	2.7	55.4	3	4	76.3	38.8	20.6	7.2	2.1	1.5†
60 minutes	0.97	93.8	6.7	57.9	7.6	11	79.7	89.8	71.5	18.3	13.2	1.9
90 minutes	0.97	91.9	4.8	56.7	5	8	78.1	89.8	70.3	17.1	12.0	
120 minutes	0.98	91.4	4.3	56.4	5	7	77.7	93.2	72.5	17.7	12.6	1.66
150 minutes	0.97	89.0	1.9	54.9	2	3	75.6	89.8	67.8	16.5	11.4	
G S, Q 26 Ht 157.5 Cm Wt, 49.8 kg Dose of glucose, 88 Gm												
Basal	0.79	76.7	0	52.2	0	0	65.2	28.6	18.6	4.5		1.0
Post glucose												
30 minutes	0.79	86.6	9.9	58.9	13	18	73.6	28.6	21.1	5.1	0.6	1.4†
60 minutes	0.94	84.2	7.5	57.3	10	14	71.6	79.6	57.0	13.9	9.4	1.8
90 minutes	1.00	83.4	6.7	56.8	9	12	70.9	100.0	70.9	17.3	12.8	
120 minutes	0.98	79.3	2.6	53.9	3	5	67.4	93.2	62.8	15.3	10.8	1.04
150 minutes	0.96	80.9	4.2	55.0	5	8	68.8	86.4	59.4	14.5	10.0	
B S, 25 Ht 157.7 Cm Wt, 48.9 Kg Dose of glucose, 86 Gm												
Basal	0.81	68.1	0	46.5	0	0	57.9	35.4	20.5	5.0		1.12
Post glucose												
30 minutes	0.88	71.9	3.8	48.9	5	6	61.1	59.2	36.2	8.8	3.8	1.74†
60 minutes	0.92	70.1	2.0	47.7	3	3	59.6	72.8	43.4	10.6	5.6	2.1
90 minutes	0.97	68.8	0.7	46.8	1	1	58.5	89.8	52.5	12.8	7.8	
120 minutes	0.95	67.7	-0.4	46.0	-1	-1	57.5	83.0	47.7	11.6	6.6	1.4
150 minutes	0.96	63.5	-4.6	43.2	-7	-9	54.0	86.4	46.7	11.4	6.4	
E R, 36 Ht 163 Cm Wt, 62.1 kg Dose of glucose, 100 Gm												
Basal	0.72	99.5	0	57.9	0	0	84.6	4.8	4.1	1.0		0.94
Post glucose												
30 minutes	0.76	104.0	4.5	60.5	4	7	88.4	18.4	16.3	4.0	3.0	1.3†
60 minutes	0.835	100.4	0.9	58.4	1	1	85.4	43.9	37.5	9.2	8.2	1.5
90 minutes	0.85	116.5	17.0	67.7	17	25	99.0	49.0	48.5	11.8	10.8	
120 minutes	0.92	96.5	-3.0	56.1	-3	-5	82.0	72.8	59.6	14.5	13.5	1.07
150 minutes	0.89	100.6	1.1	58.5	1	2	85.5	62.6	53.5	13.0	12.0	

* 15 per cent deducted from calories per hour for calories from (nitrogen) protein

† Blood sugar 15 minutes post glucose

TABLE 7—GRAMS OF CARBOHYDRATE UTILIZED BY NORMAL CONTROLS

	Name										Average
	DATA	HD	WVG	FH	BS	MC	MC	HJ	RMe	HRG	
Total gm carbohydrate utilized in 2½ hours	24.6		24.6	17.6	14.6	17.4	18.5	21.4	25.0	15.9	19.4
Dose of glucose, gm	126		126	91	90	89	95	110	137	100	
Percentage of dose utilized	19.5		19.5	19.3	16.2	19.6	19.5	19.5	18.3	15.9	18.1

fed rats on high carbohydrate diets had negligible amounts of glycogen stored in their livers, while control animals on the same diet showed large amounts. There is also some clinical evidence that points to the lack of glycogen reserve in hyperthyroidism. It has been observed that subjects with exophthalmic goiter can be sent into acidosis very easily by brief periods of fasting. A very striking example of this was seen⁵. The patient entered the hospital for the treatment of hyperthyroidism. As she had a glycosuria on general diet she was put on the "standard strict diet" (approximately 10 gm carbohydrate, 100 gm protein, 100 gm fat) in an attempt to clear up the glycosuria. She gradually went into acidosis. This was soon cleared up under carbohydrate feeding. The carbohydrate in the diet was then rapidly increased until 190 gm were given per day without appreciable quantitative change in the glycosuria. A subsequent diet with restricted carbohydrate promptly brought on an acidosis with impending coma, which was quickly cleared up by carbohydrate feeding. This suggests that the patient had a very small glycogen reserve.

TABLE 8—GRAMS OF CARBOHYDRATE UTILIZED BY SUBJECTS WITH HYPERTHYROIDISM

	Name										Average
	F B	H G	F K	O E	L M	A S	M D	G S	B S	E R	
Total gm carbohydrate utilized in 2½ hours	38.6	27.0	22.7	38.0	36.3	23.9	38.3	33.0	27.6	26.2	31.2
Dose of glucose, gm	94	84	65	92	82	72	100	88	86	100	
Percentage of dose utilized	41.1	32.2	34.9	41.3	44.3	33.2	38.3	37.5	32.1	26.2	36.1

SUMMARY

Ten normal persons and ten subjects with exophthalmic goiter have been studied under identical conditions. The blood sugar curves in the control cases were entirely normal, while those in the cases of hyperthyroidism, for the most part, showed the usual variation, i. e., an abnormally high peak maintained over a prolonged period. The respiratory quotients in the normal cases revealed normal carbohydrate storage and response while those in the cases of hyperthyroidism showed a greater and more rapid rise, which made for a striking increase in the carbohydrate utilization.

CONCLUSIONS

1. The abnormal blood sugar curves reported heretofore in cases of hyperthyroidism were found, for the most part, in our cases. Normal curves in strikingly toxic cases, however, were not unusual.

⁵ Presbyterian Hospital Surgical Service, History 30699

2 It has been shown that in hyperthyroidism, sugar, when it is offered to the tissues as a fuel, is burned with great avidity. The increased utilization of carbohydrate after carbohydrate ingestion, along with the maintained high blood sugar, points toward an inability to store glucose—most probably a failure of liver storage, due to some toxic change in the liver caused by the disease. This fits in with the results found in thyroid fed animals, and is suggested by clinical cases of exophthalmic goiter in which carbohydrate restriction is attempted.

BOOK REVIEWS

THE PRINCIPLES OF THERAPEUTICS By OLIVER T OSBORNE, M A,
M D, Professor of Therapeutics, Department of Medicine, Yale University
Pp 881 Philadelphia and London W B Saunders Company, 1921

It is, perhaps, somewhat of a surprise, certainly a pleasure, to open a textbook, entitled "The Principles of Therapeutics," and discover that only about two thirds of the text is devoted to drug therapy, while the remainder presents a consideration of therapeutic measures which are not dependent essentially on the administration of drugs. The book is intended to give the advanced student the data which he must necessarily know in order to understand the objects of scientific treatment of disease, but the plan is admittedly comprehensive and it is only by condensation and concentration that it is possible to include such a wide field in a textbook of 835 pages.

An attempt has been made to present the subject in as practical a manner as possible. The book is divided into fifteen parts, with several sections. Part I considers the art of writing prescriptions. Part II is devoted to a description of the valuable drugs and preparations of the United States Pharmacopeia with comments. Part III considers useful drugs classified according to their therapeutic action. Part IV is devoted to endocrine glands and organotherapy. Part V to practical therapeutic measures. Part VI to the use of vaccines and serums. Part VII to foods and diets. Part VIII to general physical measures. Part IX to chronic drug poisoning. Part X to industrial poisoning. Part XI to the treatment of emergencies. Part XII to the treatment of simple disturbances of the surface of the body. Part XIII to practical advice to young physicians. Part XIV to medical laws and departments of health, and Part XV to medical ethics.

The object is a worthy one but the value of the book obviously depends upon the intelligent selection of subjects for discussion and on the skill with which the relative value of different therapeutic measures is emphasized.

Part III, dealing with drug therapy, is arranged in somewhat the same manner as the therapeutic index of the valuable little volume called "Useful Drugs," published by the American Medical Association, which has its practical advantages particularly when one may go to a standard textbook on pharmacology for descriptions of drugs that are classified in the more usual manner. In reviewing this section, however, one cannot help but feel that the 280 pages devoted to it might have been enlarged with some value and at the expense of Part IV in which 112 pages are devoted to endocrine glands and organotherapy. Particularly the latter part of this section, which presents a description of the physiologic action of the prostate, thymus, pineal gland, the pancreas, spleen, liver, kidneys, parotid gland, brain, lymph nodes and bone marrow, might well have been omitted. The attempt which is made to describe the important features of modern therapy which come within the scope of the other parts of this book, is praiseworthy, but the field is so wide and the discussions on such important therapeutic measures as foods and diets and of physical methods has necessarily to be made so short that they scarcely attain their object and it is dubious whether anyone who goes to this section for information as regards the use of these measures can find more than a general statement as to their relative value and importance. Indeed he would usually have to seek further to find directions for putting them into effect. Though, therefore, at first sight the titles of these parts indicate a text of considerable practical value, one finds on careful reading that the information is only of a general nature and the concise directions which are necessary to employ many methods that are undoubtedly of considerable practical importance, are omitted.

This book can be employed, therefore, to good advantage for obtaining specific information concerning the action and use of a limited number of drugs and for general information concerning the relative value of various other therapeutic measures in the treatment of disease

PROTEIN THERAPY AND NONSPECIFIC RESISTANCE By WILLIAM F. PETERSEN, M.D., Associate in Pathology, University of Illinois, College of Medicine Chicago With an introduction by JOSEPH L. MILLER, M.D., Professor of Medicine, Rush Medical College, University of Chicago, Chicago Pp 314 New York The Macmillan Company, 1922

When one reads a book such as this, he is impressed with the great desirability of arranging some method of printing comparatively inexpensive paper bound monographs on subjects which are too new to be incorporated in a textbook and systems of medicine, and yet which through publication in medical journals are attracting general interest. A book of any size devoted to such topics, no matter how carefully prepared, rapidly becomes out of date and must be followed by a second edition or a second book which presents the subject in a more advanced stage of its development. The value of such monographs, therefore, is temporary and it should be possible to publish them as such in a readily accessible, inexpensive form.

Dr. Petersen, in this book, covers the existing knowledge concerning protein therapy and nonspecific resistance in a thorough and comprehensive manner, and one can find in this volume of 314 pages, reference to practically all the work which up to the present time has been done on this subject or has been published in closely allied fields. It is only necessary to state that the bibliography covers about fifty pages in order to give one an idea of the thoroughness with which the subject is reviewed. As is quite natural with one who has produced so much in this particular field one finds an indication throughout the book of the author's interest in the subject and his enthusiasm for the practical importance of this method of treatment, and in Chapters V and VI in which he discusses "theories concerning the mechanism of the reaction" and "the probable mechanism of the reaction," he devotes considerable space to the development of hypotheses and theories for which he himself is, in part, responsible.

In places, one is inclined to take exception to a somewhat uncritical presentation of the literature on this general subject and at times the rather unfortunate impression is produced that the author accepts in equally good faith the results of investigations made by men whose work has and has not been generally confirmed. Undoubtedly, however, this book should attract a well deserved attention for it presents in very complete form a subject about which it is difficult, without consulting a very large bibliography, to obtain any accurate information, and at the same time offers in very interesting form the author's own views as regards the theoretic action of nonspecific protein therapy and resistance.

STUDIES ON THE VISCERAL SENSORY NERVOUS SYSTEM

XIV THE REFLEX CONTROL OF THE CARDIA AND LOWER ESOPHAGUS IN MAMMALS¹

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AND
J F PEARCY
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LITERATURE

The literature on the reflex control of the cardia and lower esophagus is rather meager, in view of the importance of this question in connection with spasms of the cardia and esophagus in man. Most of the work has been done in connection with the deglutition and vomiting acts.

It was reported in a previous communication that the cardia and the lower end of the esophagus are provided with motor and inhibitory efferents both via the vagi and the splanchnic nerves.¹ We now know that in the swallowing act the vagi efferents are controlled by afferent impulses both from the pharynx (primary peristalsis) and the wall of the esophagus (secondary peristalsis).² Furthermore, the cardia and the part of the esophagus made up of smooth musculature and Auerbach's nervous plexus are capable of local coordination, that is, local automatism or reflex action, independent of afferent and efferent connections with the central nervous system.³ There has been no important contribution to the analysis of this phase of the swallowing act since the review of the subject by Cannon in 1911. But Alvarez⁴ has recently attempted to explain most, if not all, the motor phenomena of the intestine on the basis of a purely muscular gradient of rhythmicity, denying local reflexes in the intestine itself, and minimizing the importance of the extrinsic nerves in the control of the intestine. The role of the splanchnic efferents in deglutition, however, has not been studied

* From the Hull Physiological Laboratory of the University of Chicago.

1 Carlson. *Am J Physiol* **60** 14, 1922. Carlson and Luckhardt. *Am J Physiol* **57** 299, 1921.

2 Meltzer. *Am J Physiol* **2** 266, 1899, *Zentralbl f Physiol* **19** 1905.

3 Cannon. *Am J Physiol* **19** 436, 1907. *The Mechanical Factors of Digestion*, New York, 1911.

4 Alvarez. *The Mechanics of the Digestive Tract*, New York, 1922.

The reflex relation of the glossopharyngeal afferents to the esophagus is complex. Kronecker and Meltzer⁵ report that section of this nerve in animals leads to hypertonus of the esophagus lasting as long as twenty-four hours, while stimulation of the central end of the nerve may inhibit, instead of initiate, the swallowing act. Kitajew⁶ found that weak stimulation of the glossopharyngeal nerve inhibited deglutition, while strong stimulation had the opposite effect. Valenti,⁷ working on dogs without anesthesia, reports that cocaineizing (from 6 to 50 per cent) the pharynx alone, or the esophagus down to the cardia, leads to such strong and prolonged spasm of the cardia that strong efforts at vomiting induced by apomorphin cannot force food into the esophagus. Cocaineizing the vagi trunks in the neck also prevents expulsion of food by vomiting. Stimulation of the glossopharyngeal nerve, on the other hand, may induce dilation of the cardia and vomiting, with expulsion of the food from the stomach. Kronecker and Meltzer⁸ found, in man, that carbonated water in the stomach induces strong and prolonged spasm of the cardia that cannot be inhibited by deglutition. This cardiospasm is felt as a painful cramp. V. Mikulicz⁹ reported (man) that mechanical or chemical irritation of the mucosa in the region of the cardia likewise induces hypertonus of the cardia. Carbonated water and cold water in the esophagus also tend to cause hypertonus of the cardia. Cannon,³ working on cats, and using both the Roentgen ray and the Langley method for observing the tonus of the cardia, reports that acid on the stomach side increases the tonus of the cardia and thus prevents regurgitation of food into the esophagus during gastric digestion contractions. This influence of gastric acidity on the cardia obtains after section of the vagi and the splanchnic nerves. Cannon therefore regards it primarily as a local reflex.

Palugvay¹⁰ reports (man) that barium-milk passes more slowly through the cardia when the stomach is already partly filled with the mass. This may indicate that the tonus of the cardia is increased reflexly by tension in the walls of the stomach.

Openchowski¹¹ reports reflex dilatation of the cardia by stimulation of the kidneys, the uterus, the urinary bladder and the sciatic nerve. He also obtained dilatation of the cardia on stimulation of the motor area of the cerebral cortex.

⁵ Kronecker and Meltzer. *Monatschr. d. Preuss. Akad. d. Wissensch.*, 1881, p. 100.

⁶ Kitajew. (Thesis, Russian) quoted from *Jahresb. u. d. Fortschr. d. Physiol.*, 1908, p. 151.

⁷ Valenti. *Zentralbl. f. Physiol.* **20** 449, 1906, *Arch. f. Exper. Pathol. u. Pharmacol.* **63** 118, 1910.

⁸ Kronecker and Meltzer. *Arch. f. Physiol.*, 1883, Suppl. B, p. 355.

⁹ Von Mikulicz. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **12** 569, 1903.

¹⁰ Palugvay. *Arch. f. d. ges. Physiol.* **187** 233, 1921.

¹¹ Openchowski. *Zentralbl. f. Physiol.* **3** 1, 1889, *Arch. f. Physiol.*, 1889, p. 349.

Since the tonus of the cardia appears to be closely correlated to that of the stomach, we must take into account the reflex control of the latter organ in connection with the cardia. Wertheimer¹² found that sciatic stimulation caused inhibition of the stomach. This reflex was decreased by section of the vagi, but not entirely abolished by subsequent section of both the splanchnic nerves. Morat¹³ obtained inhibition of the stomach on stimulation of the central end of one vagus, provided the other vagus remained intact. Auer,¹⁴ working on rabbits, describes reflex gastric inhibition from chemical and mechanical irritation of the nasopharynx, and by irritation of the splanchnic afferents. Auer concluded that the vagi constitute the principal efferent path in this reflex. Barber and Stewart¹⁵ have recently reported contraction of the stomach (dog) from stimulation of the appendix, the gallbladder, and the duodenum.

As regards the tonus and contractions of the empty stomach (man, dog, not under anesthesia), we showed nine years ago that these are inhibited by chemical and mechanical stimulations of the nerve endings in the mouth as well as in the gastric mucosa.¹⁶ We were not able by any means to induce reflex hypertonus or contractions of the stomach in normal men and dogs by such stimuli as could be used without general anesthesia.¹⁷

EXPERIMENTAL METHODS

The methods used in this work are essentially the same as described in the report on the innervation of the mammalian cardia,¹ and the reader is referred to that paper for a more detailed description and criticism both of the mechanical devices for recording the cardia contractions and the methods of preparing the animals for experimentation. For the convenience of the reader, Figure 1 of that report is reproduced here, showing in diagram the position of the cardiometer and the devices for keeping it in place.

The animals used were cats and dogs.

One dog was provided with a permanent gastrostomy and esophageal fistula in the neck. This animal was dressed daily and otherwise well cared for, so that he is in first class condition. This dog was used for the study of reflexes to the cardia from the mouth, pharynx, and stomach, action of cocaine on the cardia, etc., without anesthesia.

12 Wertheimer. *Arch de Physiol* **4** 379, 1891.

13 Morat. *Arch de Physiol* **5** 142, 1893.

14 Auer. *Am J Physiol* **18** 347, 1907, *ibid* **25** 334, 1910.

15 Barber and Stewart. *Proc Soc Exper Biol & Med* **17** 155, 1920.

16 Carlson. *Am J Physiol* **31** 212, 1913, *ibid* **32** 389, 1913.

17 Carlson. *Am J Physiol* **35** 155, 1914. *The Control of Hunger in Health and Disease*, Chicago, 1916.

In all the acute experiments the animals were anesthetized with ether. Gastrostomy and fistula of the esophagus were made for fixing the cardiometer in place. Usually a balloon was also placed in the stomach for recording the gastric tonus. From here on the following procedures were used:

1 The experiment was conducted under constant, but light, ether anesthesia.

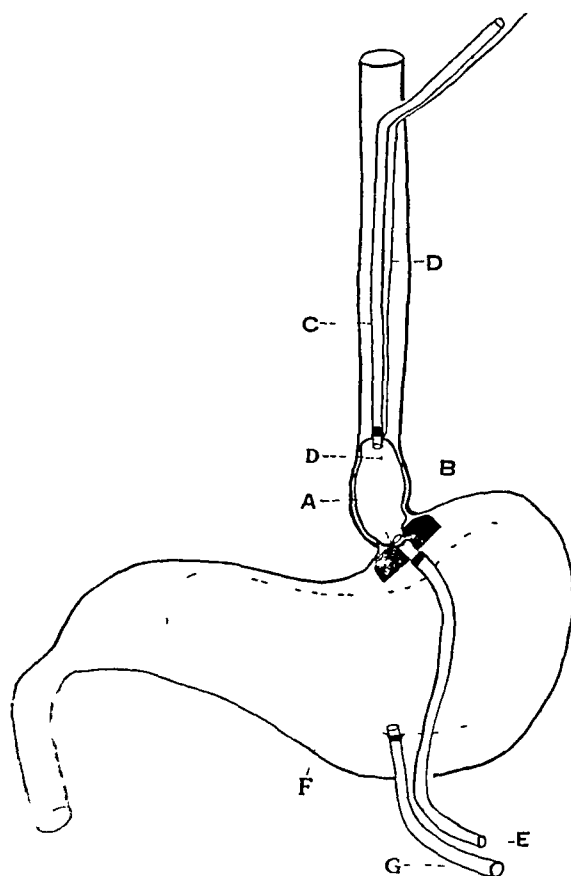


Fig 1—Diagram to illustrate method of continuous recording of the tonus of the cardia. A, (condom from 4 to 6 cm in length) in cardia and lower esophagus. B, Rubber plug (from 2 to 2.5 cm diameter, 1 cm thick), preventing cardia balloon from being pushed or pulled up into esophagus. C, Rubber tube (4 mm diameter), connecting esophageal end of cardia balloon with water manometer via esophageal fistula in neck. D, thread passing inside cardia balloon and firmly attached to rubber plug (B) for holding balloon (A) in cardia. E, rubber tube (4 mm diameter) connecting stomach end of cardia balloon with water manometer through gastric fistula. F, balloon (condom, length from 10 to 15 cm) in stomach. G, rubber tube connecting gastric balloon with water manometer through gastric fistula.

2 Ether anesthesia was continued with curare (crude extract) and artificial respiration, for elimination of skeletal and respiratory reflexes.

3 Animals were decerebrated and the ether anesthesia discontinued.

4 Conditions 1, 2 and 3 were followed with chest and respiratory mechanism intact, or with chest opened, artificial respiration, the phrenic

nerves sectioned and the diaphragm dissected away from the esophagus as completely as possible without injury to the innervation of the cardia and lower esophagus. This procedure eliminates possible errors in the tracings from contraction or spasm of the diaphragm. But it has the drawback of decreasing reflex action from "shock" due to the extensive dissection or trauma.

The following criticism may be made against procedures 1, 2 and 3.

(a) Anesthesia of sufficient depth to abolish pain and skeletal movements depresses at the same time the reflexes to the cardia. Under deep anesthesia (abolition of the lid reflex) reflexes into the cardia are abolished, or are feeble and inconstant. It is, therefore, probable that positive results under anesthesia, while correct qualitatively, are subnormal in quantity, that is, in strength and duration. But one might even question whether they are necessarily correct in quality, since ether anesthesia lowers the tonus of the cardia, and we have shown that the quality of the primary response of the cardia to stimulation of the extrinsic efferents depends on the degree of tonus of the cardia at the moment of stimulation.

(b) The anesthesia factor can be eliminated by decerebration, but handling of the visceral organs and stimulation of visceral afferents in good decerebrate preparations induces violent and prolonged skeletal movements with ultimate depression of all reflexes ("shock"). When general body movements are violent and the respiratory movements are irregular, the recording of the cardia tonus by the present method is rendered difficult.

(c) From the above considerations it would seem that the ideal preparation would be decerebration combined with curare and artificial respiration. We found, however, that crude extract of curare (Merck) in doses sufficient to paralyze the skeletal muscles for from fifteen to twenty minutes, has a direct stimulating action on the cardia and lower esophagus, inducing spasms of these regions lasting from three to fifteen minutes, and for some time after such spasm the cardia reflexes are depressed. The stronger the dose of curare the more prolonged the spasm of the cardia. And since minimal doses of curare, in cats, must be repeated every twenty or thirty minutes, curare does not leave the cardia mechanism even approximately normal. Furthermore, Klee¹⁸ reports that decerebration in cats increases the tonic action on the intestine both of the vagi and the splanchnic nerves, the former predominating.

We have obtained definite reflexes into the cardia in curarized, in decerebrated, and in curarized and decerebrated preparations, but light ether anesthesia alone yielded, on the whole, better results.

18 Klee. *Deutsch Arch f klin Med* **129** 275, 1919

The experiments that we were able to make on the dog with the permanent gastrostomy and esophageal fistula, without anesthesia, are physiologic, both in quality and quantity, as this animal was normal and in first class condition

RESULTS

A Cardia Reflexes From Skeletal Afficients—When both vagi and the splanchnic nerves are intact, stimulation of the central end of the

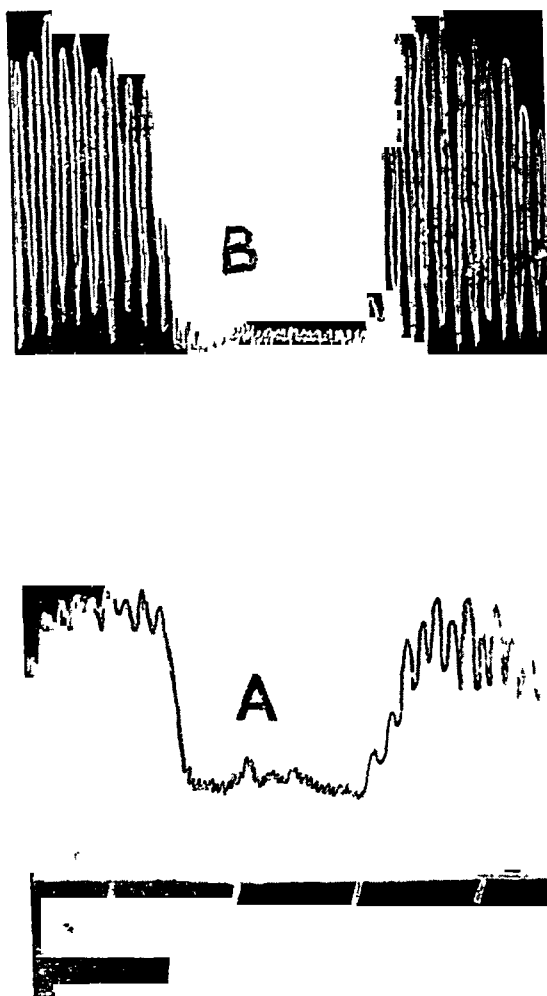


Fig 2—Cat. Light ether anesthesia. Stomach in state of digestion, but food removed through gastrostomy. Cardia and lower esophagus hypertonic, with rhythmical contractions. Water manometer tracings. A, cardia end of cardiometer. B, esophageal end of cardiometer. Signal, tetanization of central end of sciatic nerve. Showing reflex inhibition of the hypertonic cardia. Time, minutes.

sciatic nerve with the tetanizing current usually produces inhibition of the tonus of the cardia and the lower esophagus (Fig 2), as reported by Openchowski. This is particularly true if the cardia is in strong tonus. But in some experiments contraction of the cardia followed the sciaic stimulation. Both the contractions and the inhibitions usually last for a considerable period beyond the stimulation.

When both vagi are sectioned in the neck, sciatic stimulation usually causes a prolonged spasm or contraction of the cardia (Fig 3)

We have shown that, in the cat, epinephrin usually causes contraction, but it may also cause inhibition of the cardia. The question whether strong sciatic stimulation leads to an increased output of epinephrin is in dispute. But epinephrin is, at least, not solely responsible for the cardia effects here described, for they can be obtained after excision of the suprarenals. It is true that after complete suparenectomy the cardia reflexes induced by sciatic stimulation are usually

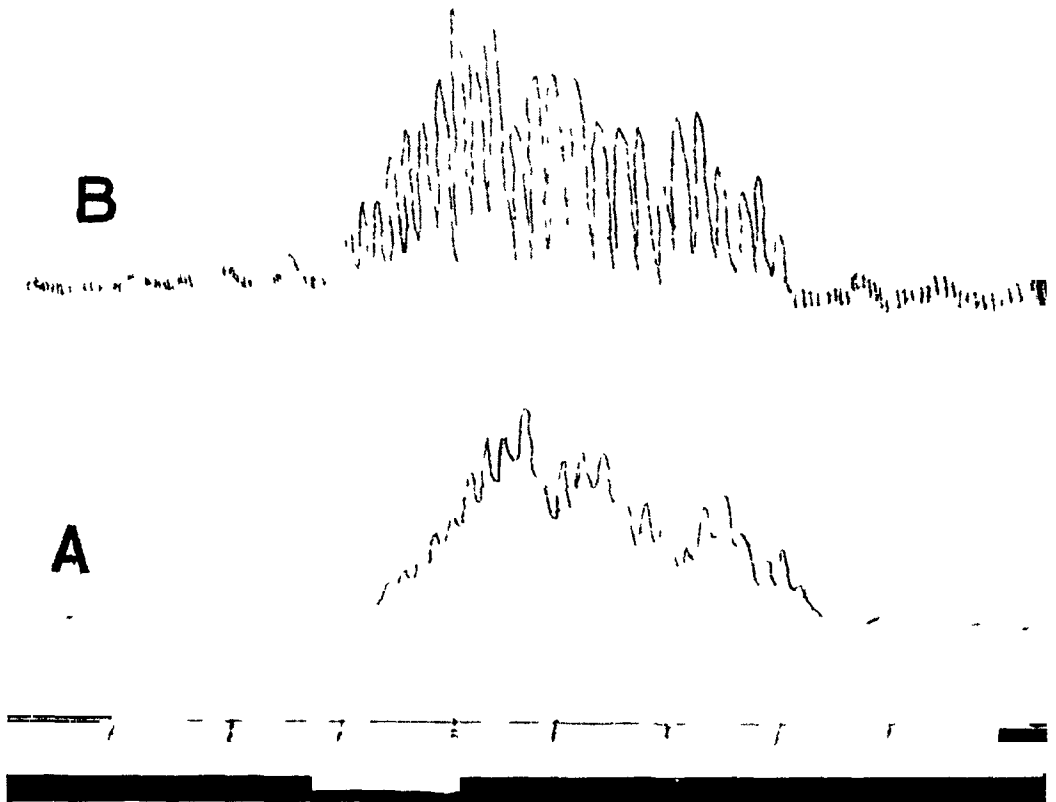


Fig 3—Cat. Light ether anesthesia. Both vagi sectioned, chest opened. Artificial respiration. Both phrenic nerves sectioned. Water manometer tracings. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. Signal, tetanization of central end of sciatic nerve. Showing reflex spasm of the cardia via the splanchnic motor efferents. Time, minutes.

less marked. But we are inclined to ascribe this to depression of the reflex centers (central and peripheral) from the trauma of the operation.

B. Cardia Reflexes From the Mouth and Pharynx.—In cats under light anesthesia mechanical, chemical, or thermal stimulation of the tongue and mouth inhibits the tonus of the cardia (Fig 4). The inhibition may be followed by increased tone at the end of the stimulation. These effects are independent of deglutition. We have obtained similar

inhibition of the cardia from the mouth in our fistula dog, but in a dog not under anesthesia it is difficult to stimulate the tongue or the mouth in any way without inducing swallowing from the increased salivation.

If the cardia is atonic, mechanical stimulation of the pharynx usually causes contraction of the cardia and lower esophagus. If the cardia is in strong tone the stimulation causes primary inhibition followed by contraction (Fig 4). Similar effects are produced by tetanization of the central end of the glossopharyngeal nerve. These reflexes are obtained in the absence of swallowing, but they fail after section of both vagi nerves.

After finding that mechanical stimulation of the pharynx, that is, of the glossopharyngeal nerve field, or tetanization of the central end of the cut glossopharyngeal nerve itself, induces opposite cardia reflexes, depending on the tonus of the cardia, we became interested in the findings of Kronecker and Meltzer, and of Valenti, that section of these nerves, or cocaineization of the pharyngeal mucosa induces permanent (many hours) hypertonus of the cardia. In acute experiments on cats we have not been able to secure the permanent hypertonus of the cardia and esophagus described by Kronecker and Meltzer as following section of both glossopharyngeal nerves. This operation cannot be made complete without some mechanical injury to the root of the vagi. Hence temporary motor disturbance of the cardia and esophagus following section of both glossopharyngeal nerves under anesthesia may be due to disturbance of the vagi.

We have repeated the experiments of Valenti of cocaineizing the pharynx of cats, under anesthesia. This procedure usually leads to some hypertonus of the cardia as reported by Valenti. But we are not satisfied that Valenti's interpretation of the fact is adequate. In the first place, it is not possible, even in light anesthesia, to cocaineize the pharynx without some of the drug reaching the esophagus, and possibly even the cardia, even when the animal does not swallow. Valenti used strong solutions of the drug (from 6 to 50 per cent). Under such conditions some of the cocaine will be absorbed from the pharynx and esophagus into the general circulation and may act on the cardia via the blood.

It is known that cocaine, in the blood, increases the action of visceral nervous mechanisms.¹⁹ We have seen that the cardia and lower esophagus have motor innervation via the splanchnic system. Numerous experiments were made on cats under ether anesthesia, and on the dog with the permanent fistulae to test this possibility of direct action of cocaine on the cardia. Intravenous injection of as little as 1 mg cocaine

19 Tatum J Pharmacol & Exper Therap 16 109, 1920

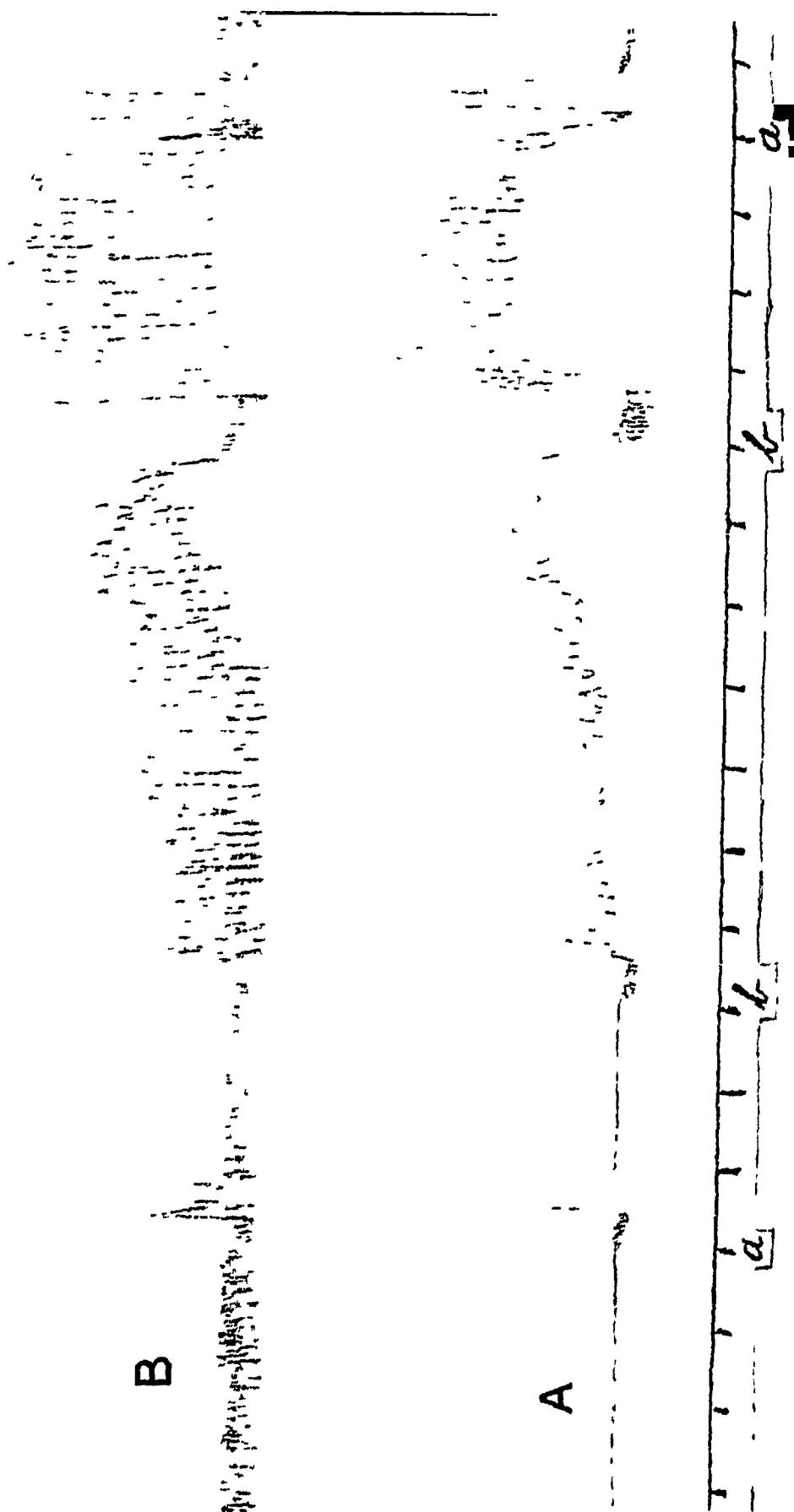


Fig 4—Cat Ether anesthesia Vagi and splanchnic nerves intact Water manometer record A, cardia opening of cardiometer B esophageal opening of cardiometer Signal a, mechanical stimulation of the tongue b mechanical stimulation of the pharyngeal mucosa Showing reflex inhibition and contraction of the cardia and esophagus from the mouth and pharynx Time, minutes

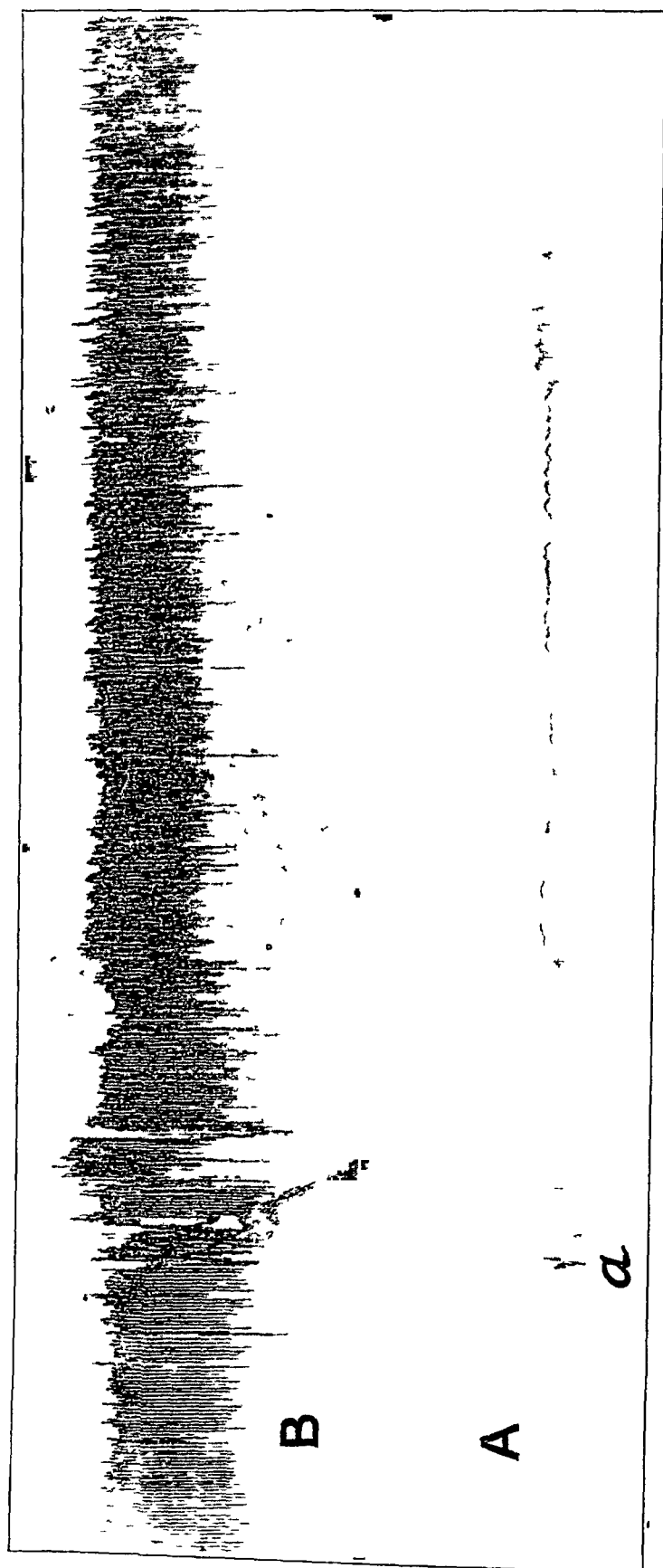


Fig 5—Dog with permanent gastrectomy and esophageal fistula No anesthesia Stomach empty Water manometer tracing
 A, cardia opening of cardiometer B, esophageal opening of cardiometer a, intravenous injection of 1 mg cocaine Showing
 increased tonus of cardia from cocaine Time, minutes

in the cat, and from 1 to 2 mg in the 15 kg dog induces distinct hypertonus of the cardia, lasting from five to fifteen minutes (Fig 5) Larger doses of the drug have more pronounced effects

Since stimulation of the glossopharyngeal nerve induces both inhibition and contraction of the cardia via the vagi efferents, and as cocaine in the blood has a direct motor action on the cardia it is evident that hypertonus of the cardia following cocaine of the pharynx is not due solely to the elimination of afferent impulses via the glossopharyngeal nerve that maintain the vagocardia inhibitory tonus in the normal animal

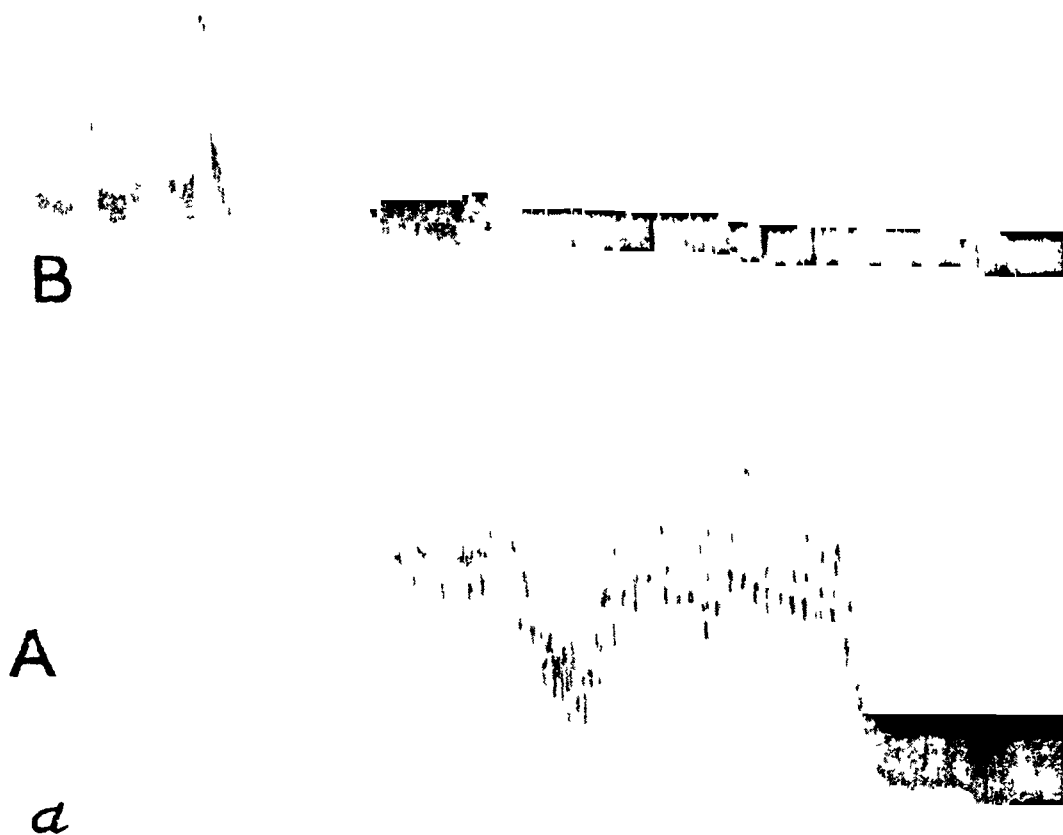


Fig 6—Cat Light ether Water manometer tracings A balloon in lower esophagus and cardia B, balloon in esophagus at level of heart a, traction on right vagus by pulling on right carotid artery, inducing spasm of the cardia

C *Cardia Reflexes via the Vagi Afferents*—The cardia and lower esophagus in cats, even under ether anesthesia, are very sensitive to mechanical stimulation of the vagi trunks in the neck The prevailing effects of traction on the intact vagus by pulling on the carotid artery is a spasm of the cardia and lower esophagus (Fig 6) This is probably partly due to mechanical stimulation of the motor fibers in the vagi, and is in part a reflex via the vagi afferents Section of the vagi produces similar spasm of the cardia (Fig 7) If one vagus is left intact stimula-



Fig 7—Cat Light ether anesthesia A, record from cardia opening of cardiometer B, record from esophageal opening of cardiometer a, section of left vagus in the neck b, beginning isolation of right vagus in neck c, section of right vagus Showing temporary spasms of lower esophagus and cardia, following section of the vagi (motor effects) Time, minutes

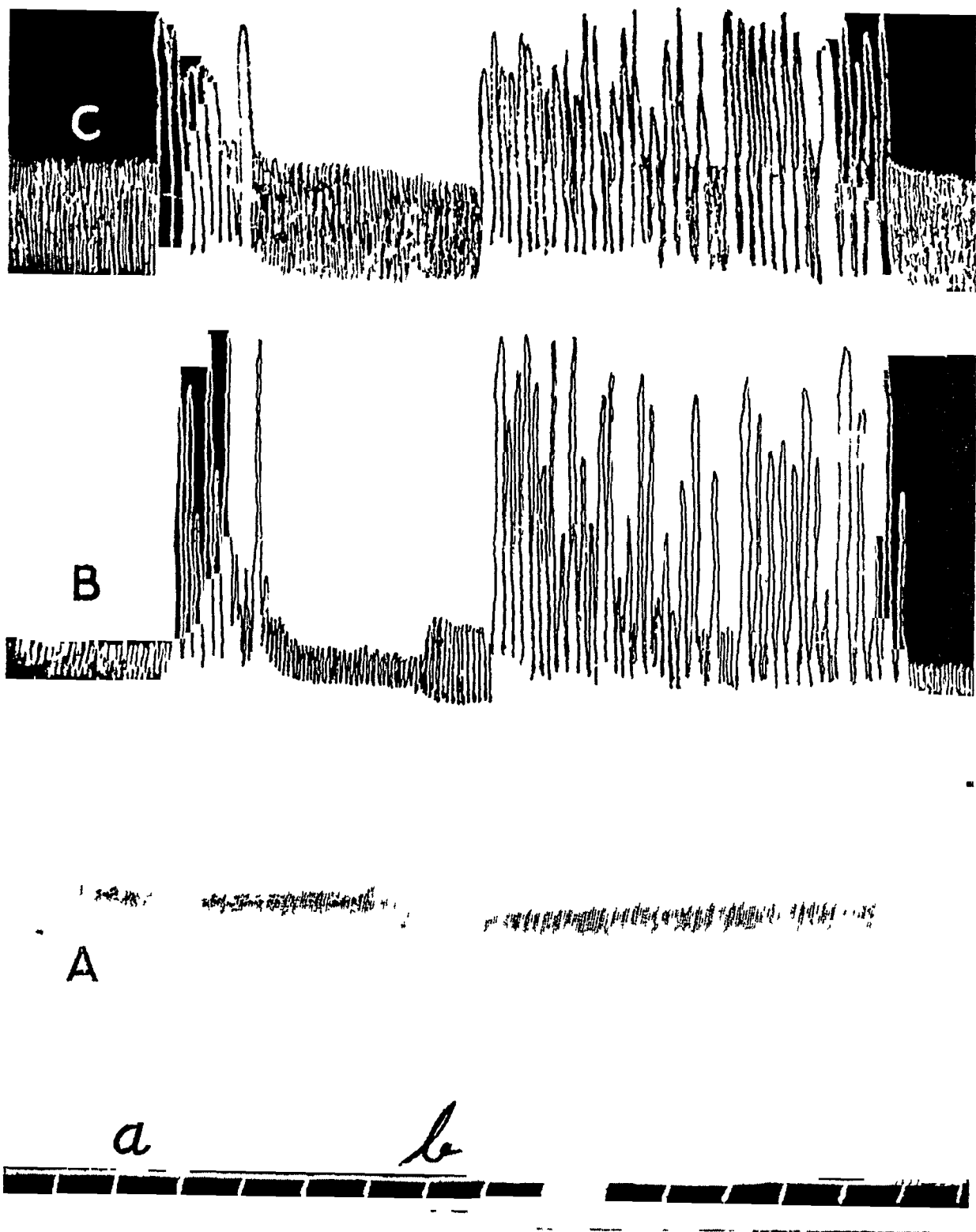


Fig 8—Decerebrated cat. Water manometer tracings. Left vagus sectioned in the neck. A, balloon in stomach. B, cardia opening of cardiometer. G, esophageal opening of cardiometer. *a*, mechanical stimulation of central end of left vagus, *b*, tetanization of central end of left vagus. Showing reflex inhibition and contraction of cardia, and inhibition of stomach, from stimulation of vagi afferents. Time, minutes.

tion of the central end of the other vagus usually causes a temporary inhibition of the cardia followed by a prolonged spasm (Fig 8) This reflex usually involves inhibition of the gastric tonus

Since the spasm of the cardia following section of the second vagus is in strength and duration similar to that induced by section of the first vagus, it is evident that this motor response is mainly due to the mechanical stimulation of the vagi motor nerve fibers to the cardia We have shown in a previous report¹ that in exceptional cases section of both vagi (cat, rabbit) leads to spasm of the cardia lasting for several hours or throughout an acute experiment Such results are difficult to explain except on the basis of a normal vagi-cardia inhibitory tonus Under the anesthesia and trauma of acute experiments this central inhibitory tonus mechanism is evidently depressed, except in an occasional preparation

In connection with Figure 7 it may be pointed out that the spasms of the cardia, induced reflexly or by direct stimulation of the motor efferents, usually appear as hypertonus with superimposed rhythmical contractions This is especially true of spasms of the cardia induced via the vagi motor efferents Direct stimulation of the splanchnic motor system may induce hypertonus of the cardia with less marked rhythmical pulsations These rhythmical contractions of the hypertonic cardia were noted over sixty years ago by Basslinger,²⁰ and are sometimes referred to as "Basslinger's pulse"

With the corresponding vagus intact, stimulation of the central end of the recurrent laryngeal nerve induces spasm of the cardia We assumed that this was a reflex, the afferent path being vagi sensory fibers from the esophagus and larynx, until in some preparations this stimulation caused contraction of the cardia even after section of both vagi nerves We feel sure that these unexpected results were not caused by escape of the electrical current to the vagus trunk or directly to the esophagus The only explanation we can suggest is that some afferent fibers from the cervical or thoracic nerves pass into the recurrent laryngeal nerve On this assumption, the contractions of the cardia following stimulation of the central end of the recurrent laryngeal nerve, with both vagi sectioned, is a reflex through the spinal cord and the splanchnic motor fibers We do not think that it is an "axon reflex," as that term is used by Langley, because the innervation of the lower esophagus and cardia by branches of the same motor neuron that supplies the esophageal muscles in the neck would render the normal peristalsis of deglutition impossible

According to experiments on dogs recently reported by Tournay,²¹ some sensory innervation of the hind legs reaches its peripheral distri-

20 Basslinger Sitzungsber Kaiserl Akad f Wissensch 38 1859

21 Tournay Compt rend Acad d sc 173 939, 1921

bution via the sympathetic system. Evidently the present views of nerve components must be reinvestigated by physiologic methods.

D Cardia Reflexes From the Stomach—In cats under light ether anesthesia and in the dog with the permanent fistula sudden stretching of the stomach wall by inflation and collapse of a condom balloon in the stomach induces hypertonus or spasms of the cardia lasting from three to ten minutes (Fig 9). This degree of distension of the empty stomach does not cause pain or distress. Similar distention of the stomach in man is felt as fullness, without distress or pain.

Our records on the dog with the permanent gastrostomy and esophageal fistula, the experiments being done without anesthesia, indicate that the hypertonicity of the cardia following sudden tension on the walls of the stomach extends to the striated musculature of the esophagus. It is, therefore, in part, a long reflex. This esophageal hypertonus is not in evidence on our cat records, the long reflexes being probably depressed by the general anesthesia.

Water, 0.4 per cent hydrochloric acid and 0.4 per cent sodium carbonate at body temperature, introduced into the stomach, induce a brief relaxation, followed by a somewhat more prolonged hypertonus of the cardia (Fig 10). There is little or no difference in the effect on the cardia from introduction of 50 to 100 cc of these fluids into the stomach through the gastrostomy. This applies to the fistula dog, where no anesthesia was used, as well as to cats under ether, except that deep anesthesia abolishes all effects on the cardia. The primary effect on the cardia, of water, acids, and alkalies, when introduced into the empty stomach, is the same as on the stomach itself, that is, inhibition.

On the basis of Cannon's observations I looked for greater increase in the cardia tonus from acid in the stomach as compared to equal volumes of water or alkalies. We have recorded elsewhere that gastric acidity fails to account for the hypertonus of the cardia during normal gastric digestion¹¹. This cardia hypertonus persists for some time after the food has been removed and the stomach washed out with water or alkalies. And the digestion hypertonus cannot be reproduced by introducing acids into the empty and quiescent stomach. It may also be noted in this connection that in the normal animal the tonus of the cardia parallels the gastric tonus, even when the stomach is empty.

These results on the cardia and lower esophagus parallel our earlier findings on the empty stomach of man and dog¹¹. The primary effect of water, acids or alkalies, introduced directly into the stomach, is a decrease in tonus and contraction of the stomach. This "receptive relaxation" is similar to that noted by Cannon as following deglutition, except that this is primarily a local action, probably reflex.



Fig 9—Dog with permanent gastrostomy and esophageal fistula (in the neck) Stomach empty Water manometer tracing A, balloon in stomach B, cardia opening of cardiometer C, esophageal opening of cardiometer, a, sudden inflation of second balloon in stomach Showing reflex spasm of the cardia and esophagus from sudden (but temporary) distention of the stomach Time, minutes

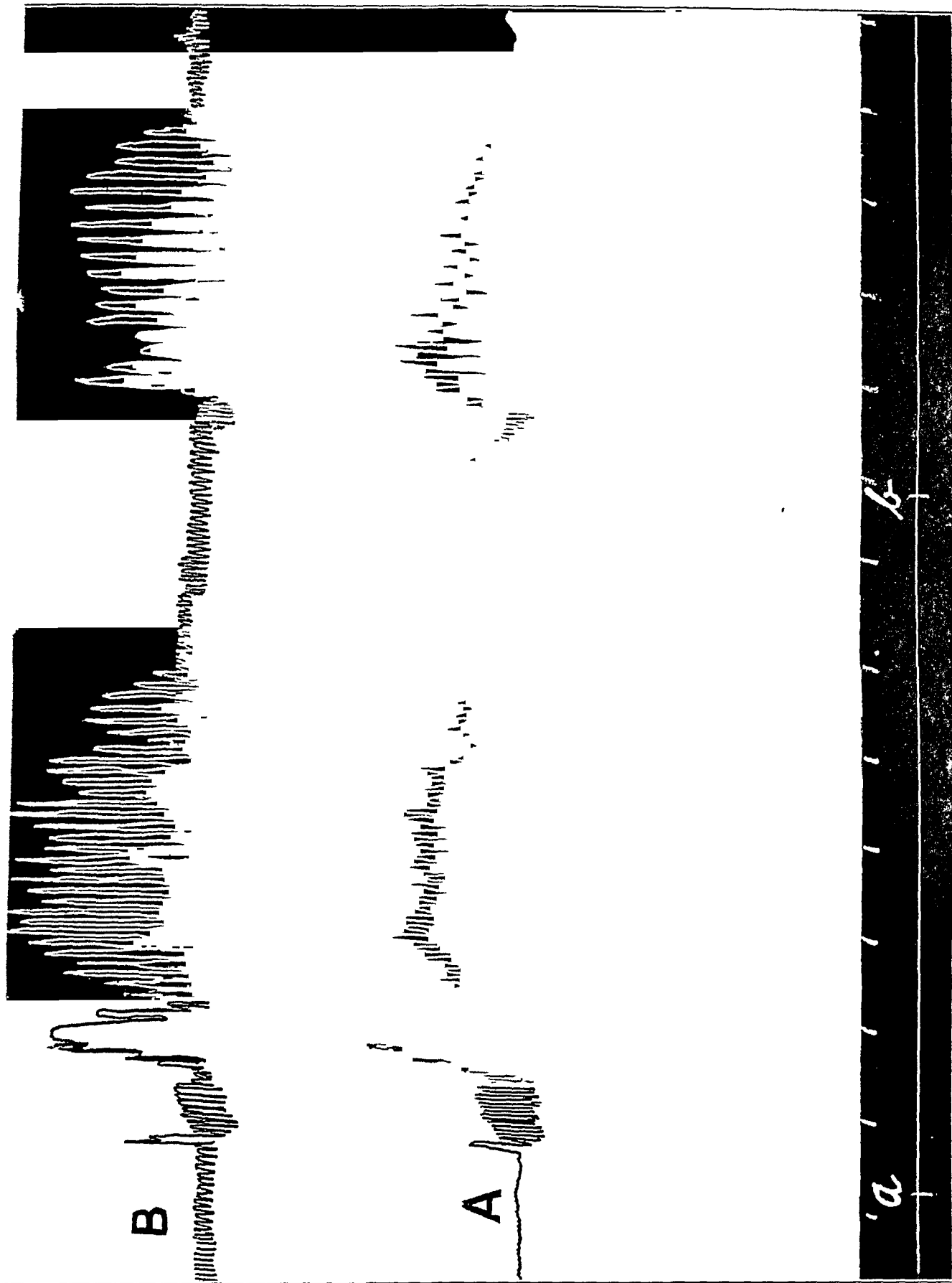


Fig 10—Cat, decerebrated. Cardia hypertonic. Water manometer tracing. A, cardia opening of cardiometer. B, esophageal opening of cardiometer. a, 50 cc of water (38 C) into the stomach, b, 50 cc 0.4 per cent hydrochloric acid (38 C) into the stomach. Showing primary cardia inhibition followed by a temporary hypertonus, from water and acid in the stomach. Time, minutes.

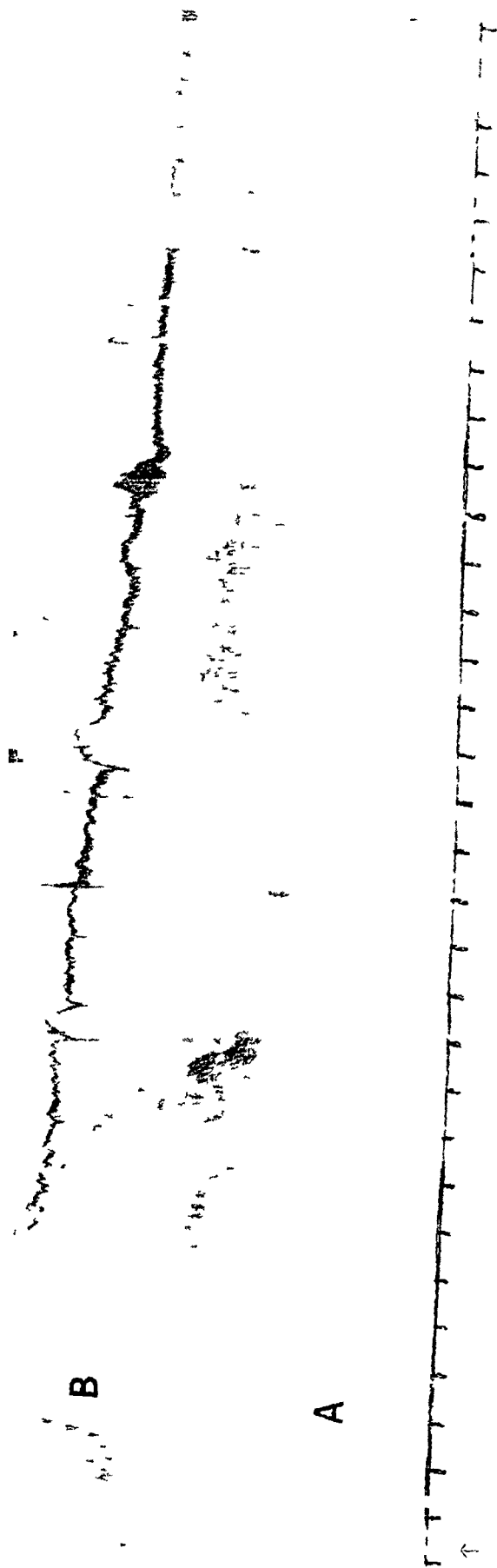


Fig 11—Cat Ether anesthesia Vagi and splanchnic nerves intact Water manometer tracing A, record from balloon in cardia B, record from esophageal balloon at level of heart ↑, pinching gallbladder with forceps Showing prolonged reflex spasm of cardia and esophagus Time, minutes

F Cardia Reflexes From the Abdominal Viscera—In decerebrated cats, as well as in cats under ether anesthesia, mechanical stimulation of the gallbladder (rubbing between the fingers, pinching with forceps) or the common bile duct leads to very marked hypertonus or spasm of the cardia, lasting at times for fifteen minutes or longer (Fig 11). This reflex is obtained, although usually in diminished degree, after section of the vagi, but not after section of both vagi and splanchnic nerves. It is, therefore, essentially a long reflex involving the vagi and splanchnic efferents. In a few experiments the gallbladder stimulation caused relaxation of the cardia. The predominance of the motor reflex



Fig 12—Cat. Light ether anesthesia. Water manometer tracing. A, balloon in lower esophagus and cardia. B, balloon in esophagus at level of heart. ↑, mechanical pressure on the urinary bladder, inducing spasm of the cardia.

may be due to the usual low tonus of the cardia in cats under anesthesia or shortly after decerebration. Electrical stimulation of the gallbladder is less efficient than the mechanical stimulation in producing the reflex spasm of the cardia.

Strong distension or compression (pinching, crushing) of the urinary bladder or of the large or small intestine induces predominantly cardia hypertonus or spasm outlasting for a long time the period of stimulation (Figs 12 and 13). The splanchnic nerves are the main afferent paths, and, in part, the efferent paths for the reflex. Very

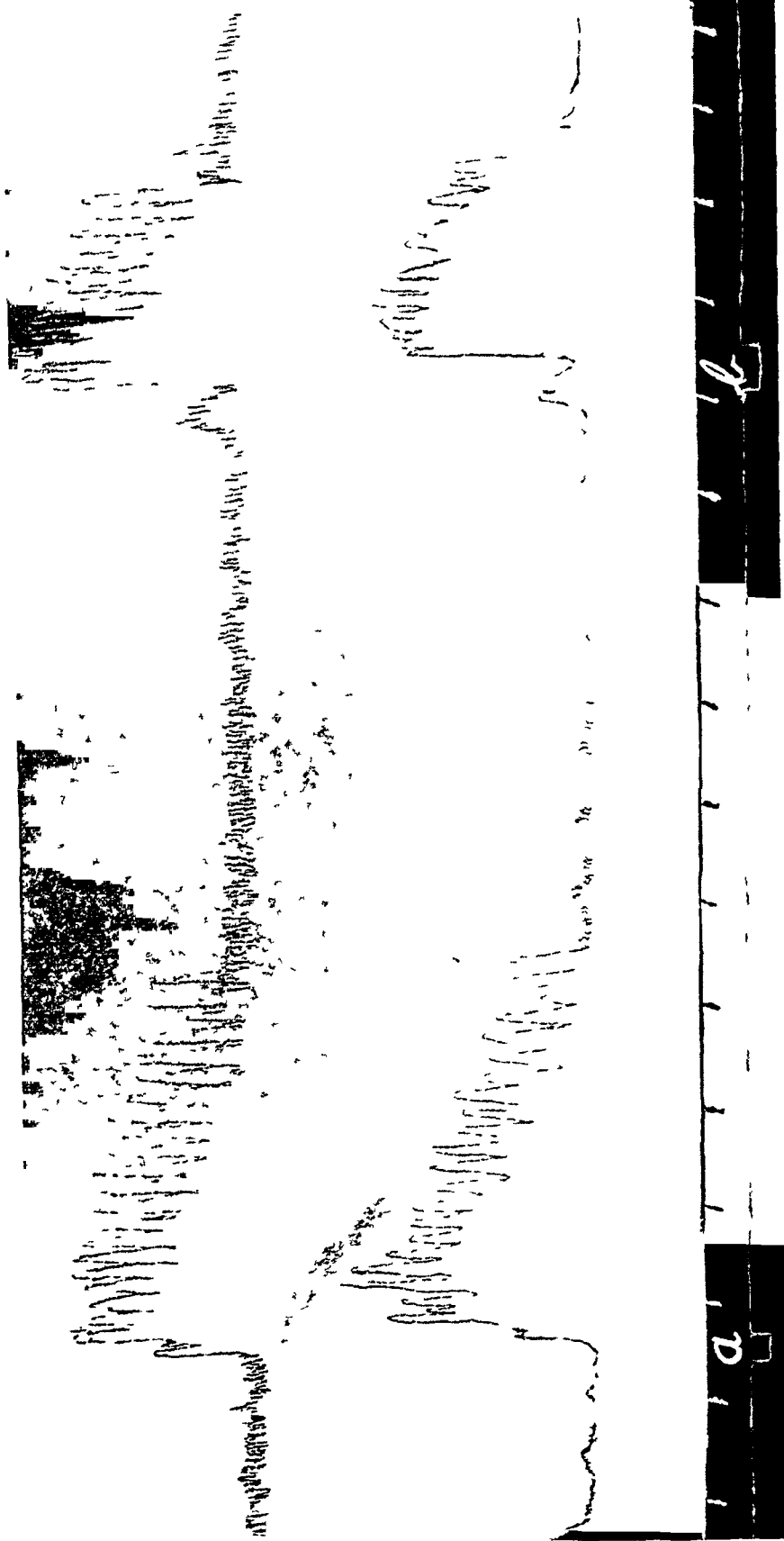


Fig 13—Cat Light ether anesthesia Water manometer tracing A, cardia opening of cardiometer B, esophageal opening of cardiometer Signal a, pressing duodenum between fingers, b, pressing large intestine between fingers Showing reflex spasm of the cardia induced by visceral afferents Time, minutes

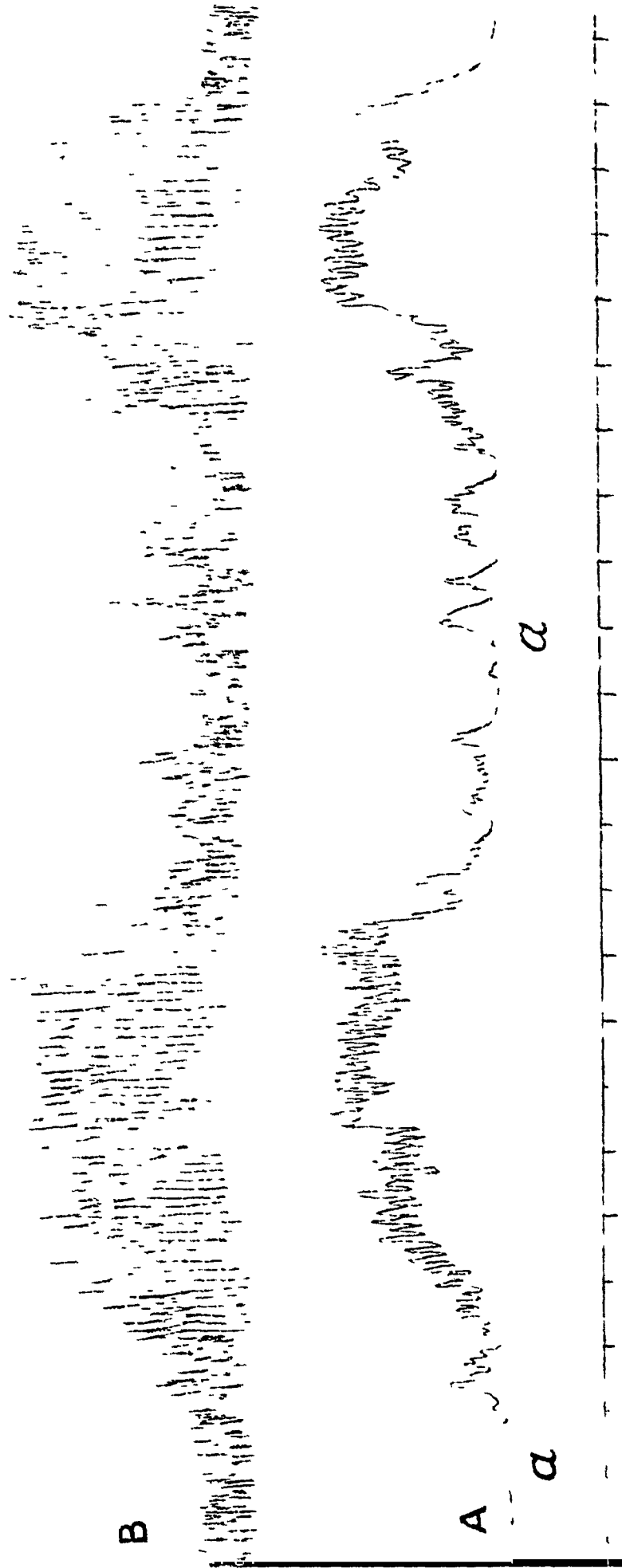


Fig 14—Cat Light ether anesthesia Water manometer tracing A, cardia opening of the cardiometer B, esophageal opening of the cardiometer a, a, traction on the central end of the left splanchnic major (sectioned) Showing reflex spasm of the cardia induced by mechanical stimulation of the splanchnic afferents Time, minutes

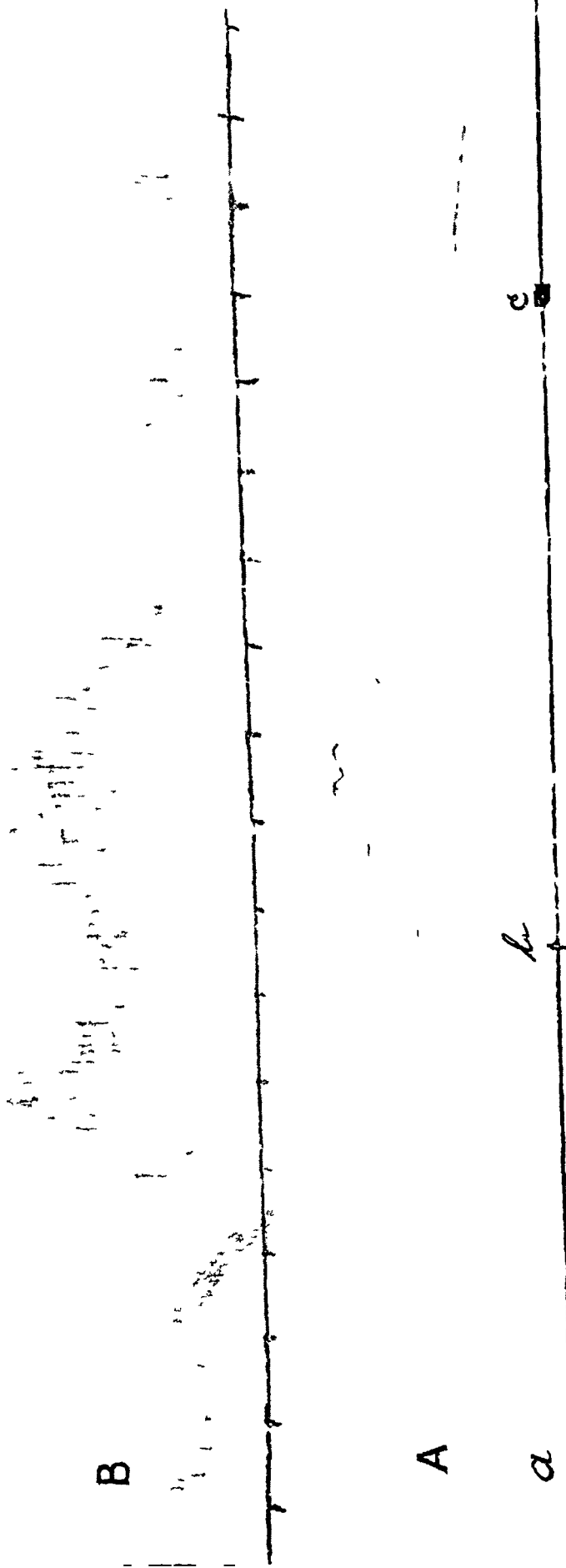


Fig 15—Cat Light ether anesthesia Both vagi sectioned in the neck Stomach empty Cardia atonic Water manometer tracing A, cardia opening of cardiometer B, esophageal opening of cardiometer *a* to *b*, isolation of left splanchnic nerves, *b*, section of left splanchnic nerve, *c*, tetanization of peripheral end of left splanchnic nerve Showing reflex and direct motor action of the splanchnic nerve on the cardia and lower esophagus Time, minutes

strong reflexes into the cardia are induced by mechanical or electrical stimulation of the central end of one splanchnic nerve (Fig 14), even after section of both vagi. The motor reflex into the cardia via the splanchnic efferents may involve stronger contraction of the cardia and lower esophagus than that caused by direct stimulation of the peripheral end of the sectional splanchnic nerve (Fig 15).

Stimulation of the sympathetic trunk in the chest, after section of the splanchnic nerves on that side, causes hypertonus or spasm of the cardia. This result is obtained even after severance of possible efferent motor nerve fibers that may enter the cardia and lower esophagus via the aortic nerve plexus. It is therefore essentially a reflex via the visceral afferents in the thoracic sympathetic trunk.

DISCUSSION

The cardia and esophageal reflexes described in the preceding sections are complex reactions, depending not only on the condition of the central nervous system, but also on the state of the intestine. The reader must not infer that all of these reflexes can be demonstrated in a single animal, even when great care is taken with the anesthesia and the trauma of necessary dissections. In some preparations the reflexes were more readily elicited than in others, even under experimental conditions as nearly identical as possible. We have no real explanation to offer for these variations, except the unknown factor of central and peripheral "shock." The motor control of the cardia and lower esophagus involves local automatism and reflexes via the Auerbach's plexus, long reflexes via the vagi efferents, and long reflexes via the splanchnic efferents. The long reflex mechanisms can, apparently, be thrown into activity by the stimulation of any sensory nerve in the body. The response of the cardia and lower esophagus in this reflex may be either relaxation or contraction, depending in part on the state of the tonus of the cardia at the time of stimulation. If the cardia is in feeble tonus, the contraction reflex prevails, if it is in strong tonus, the inhibition reflex usually predominates. But, on the whole, in our experimental conditions in the cat and dog the inhibition reflex seems to be evoked more readily via the vagi efferents, and the motor reflex via the splanchnic efferents.

While it is true that the cerebrospinal reflexes into the cardia can be initiated by the stimulation of almost any afferent nerve, nevertheless, our results indicate that the afferents from the upper end of the alimentary tract (mouth, pharynx, esophagus) and from the viscera supplied by the splanchnic system, are in the closest reflex relation to the cardia efferents. The cardia reflexes evoked by stimulation of the sensory nerves to the mucous membrane in the mouth, the pharynx,

the esophagus and the stomach are primarily inhibitory, the cardia reflexes initiated by the splanchnic afferents are predominantly motor (spasm of the cardia)

There is a long step between these types of cardia spasm induced in normal animals, under experimental conditions, and spontaneous cardiospasm in man. There is no reason for believing that the nervous control of the cardia in man is essentially different from that in the cat. But the disturbance in the afferent side of this mechanism that may lead to spasm, may apparently occur almost anywhere in the body, particularly in the viscera. Conditions leading to hyperirritability in the regions of the medulla and thoracic cord whence the motor neurons emerge will, of course, induce spasm of the cardia by excessive activity of these efferents, provided the inhibitory efferents are not rendered hyperactive at the same time. In the latter case there should be no change in the cardia control. There is some evidence of a predominant inhibitory tone of the cardia efferents, similar to the tonic action of the vagi inhibitory efferents to the heart. On this basis, spasm of the cardia could follow depression or failure of this inhibitory tonic action. Spasms of the cardia and lower esophagus would then be similar to the tachycardia due to failure of the vagus action. This is the opposite of "vagotonia," it is vagohypotonia. It is, of course, well known that cardiospasm occurs most frequently in so-called "nervous" individuals, who frequently show other evidence of defective inhibition besides tachycardia and cardiospasm.

Chronic cardiospasm is usually associated with dilation of the esophagus (striated muscular system). This may be a further indication of vagohypotonia, as the motor nerve fibers to this musculature appear to be exclusively vagal. This is, however, not an adequate explanation in all cases, since the musculature of the dilated esophagus may show actual hypertrophy or thickening. This could not take place in failure of the motor innervation, unless the striated musculature of the esophagus is less dependent on the motor nerves than are the skeletal muscles.

The fact that, in the normal man and animal at least, the tonus of the cardia is inhibited reflexly by chemical and mechanical stimulation of the sensory nerves in the mouth, may have some practical application. Bitters or acids in the mouth may reflexly help to inhibit the milder forms of reflex cardiospasm.

SUMMARY

A In normal dogs, not under anesthesia, it is shown that

1 The tonus of the cardia is temporarily inhibited by stimulation of sensory nerves in the mouth and pharynx

2 The tonus of the cardia is temporarily inhibited by stimulation of nerves in the gastric mucosa

3 The tonus of the cardia is increased by sudden distension of the walls of the stomach

4 The tonus of the cardia is increased by intravenous injection of small quantities of cocaine

5 The tonus of the cardia is increased during gastric digestion by some factor other than the acidity of the gastric contents

6 The tonus of the cardia runs parallel with the tonus and hunger contractions of the empty stomach

B In dogs and cats under light ether anesthesia, ether and curare, or decerebration, it is shown that

1 Reflex inhibition or contraction of the cardia and lower esophagus can be initiated by the stimulation of any sensory nerve, skeletal or visceral

2 When the vagi are intact stimulation of the sensory nerves in the mouth, pharynx, esophageal and gastric mucosa induces on the whole inhibition of the cardia, followed by contraction

3 Stimulation of the afferents from the abdominal viscera (gall-bladder, intestine, urinary bladder, central end of one splanchnic nerve) induces on the whole reflex contraction of the cardia and lower esophagus, even when both vagi nerves are sectioned

4 When the tonus of the cardia is feeble, the motor reflexes into the cardia predominate, when the cardia is hypertonic the inhibitory reflexes prevail

5 Strong stimulation, particularly of the abdominal viscera or the central end of the splanchnic nerve, may cause strong spasm of the cardia and lower esophagus lasting from 10 to 30 minutes

C General

1 The demonstration of motor and inhibitory innervation of the cardia and lower esophagus via the splanchnic nerves, and the confirmation and extension of Openchowski's observations on the reflex control of the cardia and lower esophagus should be taken into account in clinical cardiospasm. But it must not be inferred that the reflex spasms of the cardia here described are identical with any or all types of cardiospasm so far found in man, although it is possible that experimental chronic lesions in otherwise normal cats and monkeys may induce abnormalities in cardia control more akin to clinical cardiospasm than those revealed by the present study

ELECTROCARDIOGRAPHY AND PROGNOSIS

I SIGNIFICANT T WAVE NEGATIVITY IN ISOLATED AND COMBINED DERIVATIONS OF THE ELECTROCARDIOGRAM

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Electrocardiography has been accorded distinction as a valuable diagnostic adjunct, but as yet relatively little attention has been given to its prognostic value. I have been especially interested in the study of abnormal electrocardiograms with special reference to clinical types of heart disease and the significance of these graphic changes with regard to life expectancy. In the analysis of large groups of cases of heart disease one is impressed with the frequent occurrence of certain graphic abnormalities in definite clinical types of cardiopathies. Such cases invariably present unmistakable objective evidence of high grade myocardial disease. I am referring particularly to significant T wave negativity, to aberration of the QRS complex in all derivations of the electrocardiogram, and to the coexistence of these abnormalities. From the standpoint of prognosis, these changes constitute three well defined groups.

A very obvious fact that is brought to the attention of those who correlate large clinical and electrocardiographic data is the inability to foretell the presence or absence of these graphic changes in similarly damaged hearts.

Electrocardiography was introduced in the Mayo Clinic in 1914 and careful detailed records have been maintained of all patients examined electrocardiographically. The cases are grouped and subgrouped according to clinical and electrocardiographic types, and an automatic follow-up system of patients has been established. It is thus possible to obtain accurate mortality statistics and definitely to establish the length of life from the time of examination, and in some instances, from the onset of cardiac symptoms.

In a previous article¹ I discussed T wave negativity, its occurrence in certain isolated and combined derivations of the electrocardiogram, its occurrence in clinical types of heart disease, and the prognostic significance of certain graphic arrangements. All cases were included regardless of the association of other graphic abnormalities, particularly aberration of the QRS complex affecting all derivations.

From Division of Medicine, Mayo Clinic

¹ Willius, F. A. Observations on Negativity of the Final Ventricular T Wave of the Electrocardiogram, *Am J M Sc* **160** 844, 1920

It is my intention in this study to construct three distinct groups namely significant T wave negativity in isolated and combined derivations, aberration of the Q R S complex in all derivations, and significant T wave negativity associated with aberration of the Q R S complex in all derivations

I have called attention to two pertinent facts regarding T wave negativity, that it never occurs alone in Derivation II nor in combined Derivations I and III, and that its occurrence alone in Derivation III has no prognostic significance, since it occurs often in normal hearts and may be an inconstant phenomenon

In speaking of significant T wave negativity, I refer to the graphic arrangements, such as occurring (1) alone in Derivation I, (2) in combined Derivations I and II, (3) in combined Derivations II and III, and (4) in combined Derivations I, II, and III

Patients who have had digitalis within six weeks of the time of examination have not been included, as T wave negativity may be the result of digitalis

In this and subsequent studies the cases have been grouped according to clinical types. Control groups have been compiled for every group in this and subsequent studies. I wish clearly to define the control series to obviate any misunderstanding. In this study and in the following studies no control case is repeated. The control cases agree case for case in decade occurrence, clinical type, degree of decompensation and sex as far as possible. All the control patients had electrocardiographic study and the graphic criteria were absence of significant T wave negativity and absence of aberration of the Q R S complex in all derivations. Follow-up letters were not sent until both groups were compiled.

Study 1 comprises 449 cases and covers a period of five and one-half years. Patients are included who were examined at the Mayo Clinic up to Jan 1, 1920. It was deemed unwise to include patients of the last two years.

The graphic arrangement of significant T wave negativity in order of frequency was (1) in combined Derivations II and III, 189 cases (42.1 per cent), (2) alone in Derivation I, 146 cases (32.5 per cent), (3) in combined Derivations I and II, sixty-three cases (14.0 per cent), and (4) in combined Derivations I, II, and III, fifty-one cases (11.4 per cent).

T WAVE NEGATIVITY ALONE IN DERIVATION I (146 CASES)

A Clinical Types of Heart Disease—The myocardial degeneration associated with hypertension occurred with greatest frequency in fifty-one cases (34.9 per cent). In order of frequency the other clinical types of heart disease were angina pectoris, twenty-six cases (17.7 per cent), chronic myocarditis and chronic endocardial valvular disease

with aortic regurgitation each twenty-one cases (14.3 per cent), chronic endocardial valvular disease with mitral regurgitation, eleven cases (7.5 per cent), myocardial degeneration associated with arteriosclerosis, five cases (3.4 per cent), chronic endocardial valvular disease with aortic stenosis, four cases (2.7 per cent), myocardial degeneration associated with exophthalmic goiter and adenoma with hyperthyroidism, each three cases (2 per cent), and finally, chronic endocardial valvular disease with mitral regurgitation and stenosis, one case (0.7 per cent).

The occurrence of T wave negativity and dominance in certain clinical types of cardiac involvement will be discussed elsewhere in this paper.

B Cardiac Mortality—The subgrouping of clinical types of heart disease in this study results in some groups which are too small for comprehensive and reliable statistical conclusions yet are presented not only for their interest but for the purpose of maintaining continuity in the presentation of data. It is interesting to note, however, that the mortality averages of the smaller groups in general are confirmed by the average of the complete group.

Information regarding 115 patients has been received (Table 1). Seventy-three (63.4 per cent) have succumbed to heart disease in an average of eight and one-half months. Thirty-nine (33.9 per cent) patients are living. Nine reported their conditions improved, eighteen unchanged, and twelve worse.

In striking contrast to these data are the results in the control series (Table 2). Ninety-three patients have been heard from. Twenty-six (26.8 per cent) have died of heart disease in an average of two and four-tenths years, sixty (64.5 per cent) are living, nineteen are improved, twenty-eight are unchanged, and thirteen are worse. The difference in mortality rate is so marked and the difference in average length of life so definite that further comment is hardly necessary.

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I AND II (SIXTY-THREE CASES)

A Clinical Types of Heart Disease—In this group, as in the foregoing, the myocardial degenerations associated with hypertension dominated—twenty-three cases (36.5 per cent). The other clinical types of heart disease in order of frequency were chronic myocarditis, eleven cases (17.5 per cent), angina pectoris, nine cases (14.3 per cent), chronic endocardial valvular disease with aortic regurgitation, seven cases (11.1 per cent), chronic endocardial valvular disease with mitral regurgitation, five cases (7.9 per cent), myocardial degeneration associated with arteriosclerosis, four cases (6.3 per cent), myocardial degeneration associated with adenoma with hyperthyroidism, three cases (4.8 per cent), and myocardial degeneration associated with exophthalmic goiter one case (1.6 per cent).

B Cardiac Mortality—Forty-nine patients having T wave negativity in combined Derivations I and II of their electrocardiograms have been heard from and thirty-two (65.3 per cent) have died of heart disease in an average of twelve and seven-tenths months. Seventeen (34.6 per cent) are living. Four report their condition improved, eight unchanged, and five worse (Table 1).

In the control series of forty patients heard from, seven (17.5 per cent) of the deaths occurred from heart disease and of the twenty-nine living patients (72.5 per cent) thirteen are improved, eleven unchanged, and five worse (Table 2). Here, again, is observed a very striking difference in the mortality rates of the primary and the control series.

T WAVE NEGATIVITY IN COMBINED DERIVATIONS II AND III (189 CASES)

A Clinical Types of Heart Disease—T wave negativity in combined Derivations II and III occurred with greatest frequency in chronic myocarditis, forty-six cases (24.3 per cent). The other clinical types of heart disease, in order of frequency, were myocardial degeneration associated with exophthalmic goiter, thirty-seven cases (19.6 per cent), chronic endocardial valvular disease with mitral regurgitation, twenty-four cases (12.7 per cent), myocardial degeneration associated with hypertension, twenty-two cases (11.6 per cent), angina pectoris, sixteen cases (8.5 per cent), chronic endocardial valvular disease with aortic regurgitation, eleven cases (5.8 per cent), myocardial degeneration associated with adenoma with hyperthyroidism, ten cases (5.3 per cent), chronic endocardial valvular disease with mitral stenosis, nine cases (4.8 per cent), chronic endocardial valvular disease with mitral stenosis and regurgitation, five cases (2.6 per cent), myocardial degeneration associated with arteriosclerosis and congenital heart disease each three cases (1.6 per cent), syphilitic aortitis, two cases (1.1 per cent), and chronic endocardial valvular disease with aortic stenosis, one case (0.5 per cent).

B Cardiac Mortality—One hundred forty-nine patients in this group have been heard from, and forty-eight (32.2 per cent) have succumbed to heart disease in an average of eleven months. Ninety-two (61.7 per cent) are living and thirty-three report themselves improved, thirty-nine are unchanged, and twenty are worse (Table 1).

In the control series information regarding 110 patients has been received. Twenty-two (20 per cent) have died of heart disease in an average of one and one-half years (Table 2).

T wave negativity in combined Derivations II and III is not attended by as high a cardiac mortality as are the other groups, an observation made in my previous study.

TABLE 1—CARDIAC MORTALITY WITH SIGNIFICANT T WAVE NEGATIVITY

Clinical Classification	Total Number	Patients Heard from	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination Mos	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I													
Hypertension	51	43	37	14	1	30	69.7	10.5	12	27.9	3	2	7
Chronic myocarditis	21	19	18	3	1	10	52.6	6.8	8	42.1	2	4	2
Arteriosclerosis	5	4	5			2	50.0	8.0	2	50.0	1	1	
Angina pectoris	26	18	23	3		9	50.0	11.5	9	50.0	2	6	1
Exophthalmic goiter	3	2		3		2	100.0	4.5					
Adenoma with hyperthyroidism	3	1		3					1	100.0		1	
Mitral regurgitation	11	6	6	5		4	66.6	10.0	2	33.3		2	
Double mitral lesion	1	1	1			1	100.0	7.0					
Aortic regurgitation	21	18	19	2	1	12	66.6	10.0	5	27.7	1	2	2
Aortic stenosis	4	3	3	1		3	100.0	7.2					
Total Average	146	115	112	34	3	73	63.4	8.5	39	33.9	9	18	12
T wave Negativity in Combined Derivations I and II													
Hypertension	23	20	14	9		16	80.0	10.9	4	20.0	1	2	1
Chronic myocarditis	11	9	7	4		2	22.2	2.5	7	77.7	1	4	2
Arteriosclerosis	4	3	3	1		3	100.0	5.5					
Angina pectoris	9		9			3	50.0	30.0	3	50.0		2	1
Exophthalmic goiter	1	1		1					1	100.0	1		
Adenoma with hyperthyroidism	3		1	2									
Mitral regurgitation	5	4	5			4	100.0	9.0					
Aortic regurgitation	7		6	1		4	66.6	19.8	2	33.3	1		1
Total Average	63	49	45	18		32	65.3	12.7	17	34.6	4	8	5
T wave Negativity in Combined Derivations II and III													
Hypertension	22	16	16	6		10	62.5	14.5	6	37.5		3	3
Chronic myocarditis	46	35	25	21	1	7	20.0	20.0	27	77.1	6	12	9
Arteriosclerosis	3	2	1	2		1	50.0	0.75	1	50.0	1		
Angina pectoris	16	15	16			10	66.6	9.3	5	33.3	2	3	
Exophthalmic goiter	37	28	7	30	3	3	10.7	16.6	22	78.5	17	3	2
Adenoma with hyperthyroidism	10	10	3	7					10	100.0	6	1	3
Mitral regurgitation	24	19	8	16	2	11	57.8	9.8	6	31.5	1	3	2
Mitral	9	6		9	1	1	16.6	1.0	4	66.6		4	
Double	5	5	1	4	1	3	60.0	16.6	1	100.0		1	
Aortic	11	9	9	2	1	2	22.2	?	6	66.6		6	
Aortic stenosis	1	1		1					1	100.0			1
Syphilitic aortitis	2	1	1	1					1	100.0		1	
Congenital heart disease	3	2		3					2	100.0		2	
Total Average	189	149	87	102	9	48	32.2	11.0	92	61.7	33	39	20
T wave Negativity in Combined Derivations I, II, and III													
Hypertension	14	11	12	2	2	9	81.8	11.5					
Chronic myocarditis	8	6	4	4		2	33.3	24.0	4	66.6		2	2
Arteriosclerosis	1	1	1			1	100.0	?					
Angina pectoris	7	6	6	1		5	83.3	39.7	1	16.6		1	
Exophthalmic goiter	2	2	2						2	100.0	1	1	
Adenoma with hyperthyroidism													
Mitral regurgitation	5	1		2					1	100.0	1		
Aortic regurgitation	9	4	5		1	2	50.0	2.0	1	25.0			1
Double aortic lesion	2	6	9			3	50.0	8.0	3	50.0		3	
Congenital heart disease	1	1	1	1		2	100.0	9.5					
Total Average	51	40	41	10	3	27	62.5	12.7	12	20.0	2	7	3
Grand total Grand average	449	333	285	164	15	178	70.4	11.2	100	45.3	48	72	40

TABLE 2—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living					
			Males	Females		Number	Percentage	Average Time Since Examination Mos	Number	Percentage	Improved	Unchanged	Worse	
T wave Negativity in Derivation I														
Hypertension	51	35	21	30	2	11	31.4	14.3	22	62.8	4	11	7	
Chronic myocarditis	21	14	14	7		4	28.0	31.2	10	71.0	5	3	2	
Arteriosclerosis	5	4	5						1	100.0	1	3		
Angina pectoris	26	22	19	7	1	7	31.8	?	14	63.6	6	7	1	
Exophthalmic goiter	3	3		3					3	100.0	1	1	1	
Adenoma with hyperthyroidism	3	1		3					1	100.0	1			
Mitral regurgitation	11	5	4	7	1	1	20.0	?	3	60.0	1	1	1	
Double mitral lesion	1	1	1	1										
Aortic regurgitation	21	6	15	6	1	2	33.3	?	3	50.0		2	1	
Aortic stenosis	4	2	2	2	1	1	50.0	42.0						
Total Average	146	93	81	65	7	26	36.8	28.8	60	64.5	19	28	13	
T wave Negativity in Combined Derivations I and II														
Hypertension	23	13	13	10	3	2	15.3	4.5	8	61.5	4	2	2	
Chronic myocarditis	11	8	6	5		2	25.0	6.5	6	75.0	1	5		
Arteriosclerosis	4	4	3	1		1	25.0	36.0	3	75.0	3			
Angina pectoris	9	5	8	1	1				4	80.0	2	2		
Exophthalmic goiter	1			1										
Adenoma with hyperthyroidism	3	2		3					2	100.0		1	1	
Mitral regurgitation	5	4	5			1	25.0	7.0	3	75.0	1	1	1	
Aortic regurgitation	7	4	5	2		1	25.0	?	3	75.0	2		1	
Total Average	63	40	40	23	4	7	17.5	10.8	29	72.5	13	11	5	
T wave Negativity in Combined Derivations II and III														
Hypertension	22	11	15	7		4	36.3	9.7	7	63.6	4		3	
Chronic myocarditis	16	29	27	19	2	5	17.2	20.4	22	75.8	9	10	3	
Arteriosclerosis	3	1	3		1									
Angina pectoris	10	10	12	4		2	20.0	24.0	8	80.0		8		
Exophthalmic goiter	37	24	3	34	1				23	95.8	16	5	2	
Adenoma with hyperthyroidism	10	6		10					6	100.0	3	3		
Mitral regurgitation	24	14	12	12	2	7	50.0	15.8	5	35.7	1	2	2	
Mitral stenosis	9	5	3	6		2	40.0	9.5	3	60.0		1	2	
Double mitral lesion	5	2	3	2		1	50.0	22.0	1	50.0	1			
Aortic regurgitation	11	4	8	3		1	25.0	36.0	3	75.0	1	2		
Aortic stenosis	1			1										
Syphilitic aortitis	2	1	1	1					1	100.0	1			
Congenital heart disease	3	3		3					3	100.0		2	1	
Total Average	189	110	87	102	6	22	20.0	18.0	82	74.5	36	33	13	
T wave Negativity in Combined Derivations I, II, and III														
Hypertension	14	10	5	9		1	10.0	42.0	9	90.0	3	6		
Chronic myocarditis	8	6	4	4	1	5	50.0	13.0	2	33.3	1	1		
Arteriosclerosis	1	1	1						1	100.0	1			
Angina pectoris	7	6	7			2	33.3	2.7	4	66.6	1	3		
Exophthalmic goiter	2	1	2						1	100.0	1			
Adenoma with hyperthyroidism	2	2		2					2	100.0	1	1		
Mitral regurgitation	5	3	2	3	1				2	66.6	1	1		
Aortic regurgitation	9	7	6	3	1	2	28.5	?	4	57.1	1	3		
Double aortic lesion	2	2	1	1					3	100.0		1	1	
Congenital heart disease	1	1	1						1	100.0		1		
Total Average	51	39	29	22	3	8	20.5	19.2	28	71.7	10	17	1	
Grand total Grand average	449	282	237	212	20	63	22.3	19.2	199	70.5	78	89	32	

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I, II, AND III
(FIFTY-ONE CASES)

A *Clinical Types of Heart Disease*—Myocardial degeneration associated with hypertension as in the first two groups dominates the clinical types of heart disease in T wave negativity in combined Derivations I, II and III. The other types in order of frequency were chronic endocardial valvular disease with aortic regurgitation, nine cases (17.6 per cent), chronic myocarditis, eight cases (15.7 per cent), angina pectoris, seven cases (13.7 per cent), chronic endocardial valvular disease with mitral regurgitation, five cases (9.8 per cent), myocardial degeneration associated with exophthalmic goiter, adenoma with hyperthyroidism and chronic endocardial valvular disease with aortic regurgitation, and stenosis, each two cases (3.9 per cent), and finally, myocardial degeneration associated with arteriosclerosis and congenital heart disease, each one case (2 per cent).

B *Cardiac Mortality*—Forty patients have been traced and twenty-five (62.5 per cent) have died of heart disease in an average of twelve and seven-tenths months. Twelve patients (30 per cent) are living, two are improved, seven are unchanged, and three are worse.

In the control series thirty-nine patients have been heard from and eight (20.5 per cent) have died of heart disease. Twenty-eight (71.7 per cent) are living, ten are improved, seventeen are unchanged, and one patient is worse. This, again, is an instance of marked difference in cardiac mortality.

It is interesting to note how constant the cardiac mortality in the control series runs.

DISCUSSION

There can be no question with regard to the prognostic importance of significant T wave negativity. As I have said, the effect of digitalis must always be borne in mind and such cases of T wave negativity are inconstant and obviously do not fall in the category of the types under discussion. One is impressed with the constant association of significant T wave negativity and clinical evidence of serious cardiac disease.

I wish to call attention again to Table 1 and to the description of clinical types of heart disease which clearly depicts the dominance of conditions of the degenerative type. Foremost among them is the hypertension group, notorious for its attendant vascular degeneration. Chronic myocarditis extensively involving the musculature of the heart unquestionably affects the vascular elements of the organ. Likewise angina pectoris is constantly associated with vascular disease. Aortic regurgitation with its usual attendant aortitis has also a definite vascular basis.

Significant T wave negativity in all probability occurs in hearts involved by intrinsic vascular degeneration of the obliterative type. All our evidence at the present time suggests this theme and is based on clinical, pathologic, and experimental study. The high and early cardiac mortality rate attending significant T wave negativity implies a progressive disease process and further supports the foregoing concept.

Cardiac histopathology has failed miserably in attempting to explain and to clarify diseases of the myocardium. Conclusions have been based entirely on the presence or absence of actual tissue changes and no attention has been given to physiologic abnormalities. Only a few years ago a controversy arose regarding the causation of a certain electrocardiographic condition, and the arguments pro and con were based entirely on the presence or absence of gross and microscopic myocardial changes. One observer, by means of serial sections, demonstrated constant lesions in the heart muscle attending his bizarre graphs, and the other, by the same means, failed to find the tissue changes. Both sides of this controversy were seeking for the effect and not for the cause of the graphic anomalies, and we have many reasons to believe that a careful study of the vascular tree of the heart would have resulted in agreement. The presence of actual changes in the myocardium certainly is not necessarily a constant finding even though intrinsic vascular disease exists. With this concept in mind it is obvious that physiologic disturbances may often precede histopathologic changes.

SUMMARY

The cardiac mortality attending significant T wave negativity is high and is in sharp contrast to that in the control series. In order of importance the cardiac mortality is as follows:

T wave negativity in combined Derivations I and II, 65.3 per cent in 127 months. Control series, 17.5 per cent in 108 months.

T wave negativity alone in Derivation I, 63.4 per cent in 85 months. Control series, 26.8 per cent in 24 years.

T wave negativity in combined Derivations I, II and III, 62.5 per cent in 127 months. Control series, 20.5 per cent in 192 months.

T wave negativity in combined Derivations II and III, 32.2 per cent in 110 months. Control series, 20.0 per cent in 15 years.

Total of significant T wave negativity, 50.4 per cent in 112 months. Total of control series, 22.3 per cent in 192 months.

II ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS OF THE ELECTROCARDIOGRAM *

Aberrations of the QRS complex of the electrocardiogram involving all derivations have been the subject of considerable controversy. The variance of views has largely involved histopathologic issues. The

observer who has often noted this electrocardiographic abnormality and has correlated his graphic and clinical data is impressed with the gravity of the underlying cardiac disease

In this group of cases, as in significant T wave negativity, an obliterative intrinsic vascular basis is strongly suggested

Aberration of the Q R S complex of the electrocardiogram is characterized by notching of the apex, ascending or descending limb and in the complex of unaltered contour, a base width exceeding 0.10 second. The bizarre complex of high amplitude and diphasic in form is ascribed to bundle branch block while no definite localization is justifiable in the monophasic complex of lower amplitude

TABLE 1—CARDIAC MORTALITY WITH ABERRATION OF THE Q R S COMPLEX IN ALL DERIVATIONS

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos	Number	Percentage	Improved	Unchanged	Worse
Hypertension	17	10	9	8		8	80.0	18.3	2	20.0		2	
Chronic myocarditis	29	21	19	10	1	9	42.8	6.6	11	52.4	2	5	-
Arteriosclerosis	15	13	12	3		10	76.9	23.6	3	23.0	1	2	
Angina pectoris	10	9	7	3		6	66.6	23.1	3	33.3		3	
Exophthalmic goiter	7	5	1	6		3	60.0	?	2	40.0	1	1	
Adenoma with hyperthyroidism	9	8		9	1	3	37.5	7.7	4	50.0	2	1	1
Mitral regurgitation	10	6	8	2	1	5	83.3	12.5					
Double mitral lesion	3	3	1	2		1	33.3	15.0	2	66.6		1	1
Mitral stenosis	2	1	2			1	100.0	7.0					
Aortic regurgitation	10	5	9	1		5	100.0	?					
Total Average	112	81	68	44	3	51	62.9	14.2	27	33.3	6	15	6

I have previously emphasized¹ the constant association of this graphic abnormality with serious and advanced heart disease and have shown the high and early cardiac mortality, occurring in this group. The cases presented were associated in many instances with significant T wave negativity, but those cases have not been included in this report.

This study comprises 112 cases covering a period of five and one-half years. The control series has been compiled based on the same conditions as in the foregoing study.

A Clinical Types of Heart Disease (112 Cases)—Chronic myocarditis occurred with greatest frequency, twenty-nine cases (25.9 per cent). The other clinical types of heart disease in order of frequency were the myocardial degeneration associated with hypertension, seventeen cases (15.2 per cent), myocardial degeneration associated with arterio-

sclerosis, fifteen cases (13.4 per cent), angina pectoris, chronic endocardial valvular disease with mitral regurgitation, and aortic regurgitation, each ten cases (8.9 per cent), myocardial degeneration associated with adenoma with hyperthyroidism, nine cases (8 per cent), exophthalmic goiter, seven cases (6.3 per cent), chronic endocardial valvular disease with mitral regurgitation and stenosis, three cases (2.7 per cent), and finally, chronic endocardial valvular disease with mitral stenosis, two cases (1.8 per cent). It is quite evident that degenerative diseases also dominate this group.

B Cardiac Mortality—Information has been obtained regarding eighty-one patients and fifty-one (62.9 per cent) have died of heart

TABLE 2—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination in Months	Number	Percentage	Improved	Unchanged	Worse
Hypertension	17	9	8	9	1	1	11.1	3.0	7	77.7	3	4	
Chronic myocarditis	29	14	20	9	3	4	28.5	17.5	7	50.0	2	5	
Arteriosclerosis	15	9	14	1		2	22.2	33.0	7	77.7	1	6	
Angina pectoris	10	6	6	4	1	2	33.3	5.0	3	50.0	1	2	
Exophthalmic goiter	7	5	1	6					5	100.0	2	3	
Adenoma with hyperthyroidism	9	5	1	8					5	100.0	3	2	
Mitral regurgitation	10	6	7	3		3	50.0	3.5	3	50.0		3	
Double mitral lesion	3	2	2	1	1				1	50.0	1		
Mitral stenosis	2	2	1	1					2	100.0	1		1
Aortic regurgitation	10	7	8	2		2	28.5	20.0	5	71.4		3	2
Total Average	112	65	68	44	6	14	21.5	13.7	45	69.2	14	28	3

disease in an average of fourteen and two-tenths months. Twenty-seven (33.3 per cent) patients are living and of these, six are improved, fifteen are unchanged, and six are worse (Table 1).

In striking relief to these averages are the results of the control series. Sixty-five patients have been heard from, and only fourteen (21.5 per cent) have succumbed to heart disease in an average of thirteen and seven-tenths months. Forty-five (69.2 per cent) are alive, fourteen are improved, twenty-eight are unchanged, and three are worse (Table 2).

DISCUSSION

The great difference in cardiac mortality between cases exhibiting aberration of the Q R S complex in all derivations of the electrocardiogram and identical clinical types of cardiac disease in which this graphic abnormality does not exist is convincing. The only justifiable criticism that is apparent to me is the reliability of the control series. In Study I,

I have defined the criteria for all the control groups and have shown that in all respects except an accurate sex agreement the controls were identical case for case exclusive, of course, of the electrocardiographic changes under discussion

The early and high mortality is indicative of a progressive process and, as previously stated, favors the concept of obliterative intrinsic vascular disease

SUMMARY

The cardiac mortality attending aberration of the Q R S complex in all derivations of the electrocardiogram practically trebles that of the control series

Aberrant Q R S complexes in all derivations, cardiac mortality, 62.9 per cent in 142 months

Control series, cardiac mortality, 21.3 per cent in 137 months

NOTE—No attempt has been made to record a complete bibliography dealing with aberration of the Q R S complex as the pros and cons of the arguments regarding this abnormality are already recorded in most of the previous publications dealing with this subject

III SIGNIFICANT T WAVE NEGATIVITY AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS OF THE ELECTROCARDIOGRAM

The foregoing studies have emphasized the prognostic importance of significant T wave negativity and of aberration of the Q R S complex occurring in all derivations of the electrocardiogram. This study is of cases in which these graphic abnormalities occurred together. With the preceding statistics in mind it is reasonable to anticipate a greater cardiac mortality in this study. Patients exhibiting both electrocardiographic abnormalities generally have more marked subjective and objective evidence of cardiac damage than those in whom these graphic changes occur separately.

One hundred and thirty-five cases are included in this study which covers a period of five and one-half years.

The control groups are based on the criteria of those in the preceding groups.

T WAVE NEGATIVITY ALONE IN DERIVATION I AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (NINETY CASES)

A Clinical Types of Heart Disease—The myocardial degeneration associated with hypertension occurred with greatest frequency, thirty-five cases (38.9 per cent). The other types in order of frequency were chronic myocarditis, twenty-two cases (24.4 per cent), chronic endocardial valvular disease with aortic regurgitation, eight cases (8.9

per cent), angina pectoris, seven cases (78 per cent), myocardial degeneration associated with arteriosclerosis and chronic endocardial valvular disease with mitral regurgitation, each five cases (56 per cent), adenoma with hyperthyroidism, four cases (44 per cent) and exophthalmic goiter, one case (11 per cent)

B Cardiac Mortality—Information regarding seventy-three patients has been received and sixty-three (86.3 per cent) have died of heart disease in an average of eight and four-tenths months following examination. Seven patients (9.5 per cent) are alive and of these two are improved, two are unchanged, and three are worse (Table 1)

The control group sharply contrasts this mortality. Sixty patients have been heard from and eighteen (30 per cent) have succumbed to heart disease in an average of twenty-one and four-tenths months following examination. Thirty-eight (63.3 per cent) are living and eleven report their condition improved, twenty-two unchanged, and five worse (Table 2)

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I AND II AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (TWENTY-THREE CASES)

A Clinical Types of Heart Disease—Myocardial degeneration associated with hypertension again is an outstanding condition, twelve cases (52.2 per cent). The other clinical types in order of frequency are chronic myocarditis and chronic endocardial valvular disease with aortic regurgitation each, three cases (13 per cent), angina pectoris and chronic endocardial valvular disease with mitral regurgitation each, two cases (8.7 per cent), and aortic aneurysm, one case (4.3 per cent)

B Cardiac Mortality—Twenty patients have been traced and all but one have died of heart disease (95 per cent) in an average of eight and one-half months following examination. The surviving patient (5 per cent) is worse (Table 1)

In the control group facts regarding sixteen patients have been received. Three (18.7 per cent) have died of heart disease in an average of six and seven-tenths months following examination. Of the nine living patients (56.2 per cent) six are unchanged and three are worse (Table 2)

—

T WAVE NEGATIVITY IN COMBINED DERIVATIONS II AND III AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS (SEVENTEEN CASES)

A Clinical Types of Heart Disease—Chronic myocarditis occurred with greatest frequency, five cases (29.4 per cent). The other types

TABLE 1—CARDIAC MORTALITY WITH SIGNIFICANT T WAVE NEGATIVITY AND ABERRATION OF THE QRS COMPLEX IN ALL DERIVATIONS

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
			Males	Females		Number	Percentage	Average Time Since Examination, Mos	Number	Percentage	Improved	Unchanged	Worse
T wave Negativity in Derivation I and Aberration of the QRS Complex in all Derivations													
Hypertension	35	28	22	13	2	23	82.1	15.4	3	10.7		1	2
Chronic myocarditis	22	16	17	5		15	93.7	9.0	1	6.2		1	
Arteriosclerosis	5	4	4	1		3	75.0	0.9	1	25.0			1
Angina pectoris	7	5	6	1		5	100.0	2.4					
Exophthalmic goiter	1	1		1					1	100.0	1		
Adenoma with hyperthyroidism	4	4	1	3	1	3	75.0	18.0					
Mitral regurgitation	5	4	3	2		3	75.0	?	1	25.0	1		
Double mitral lesion	3	2	2	1		3	100.0	3.2					
Aortic regurgitation	8	8	8			8	100.0	9.8					
Total Average	90	73	63	27	3	63	86.3	8.4	7	9.5	2	2	3
T wave Negativity in Combined Derivations I and II and Aberration of the QRS Complex in all Derivations													
Hypertension	12	11	10	2		11	100.0	12.8					
Chronic myocarditis	3	2	2	1		2	100.0	1.7					
Angina pectoris	2	2	2			2	100.0	5.0					
Mitral regurgitation	2	1	1	1		1	100.0	11.0					
Aortic regurgitation	3	3	3			3	100.0	12.0					
Aortic aneurysm	1	1	1						1	100.0			1
Total Average	23	20	19	4		19	95.0	8.5	1	5.0			1
T wave Negativity in Combined Derivations II and III and Aberration of the QRS Complex in all Derivations													
Hypertension	3	2	2	1		2	100.0	?					
Chronic myocarditis	5	5	4	1		2	40.0	13.0	3	60.0	1	2	
Arteriosclerosis	1	1	1			1	100.0	20.0					
Angina pectoris	3	3	3			2	66.6	37.2	1	33.3			
Mitral regurgitation	2	2	2	1		2	100.0	20.5					
Double mitral lesion	1	1	1			1	100.0	3.0					
Aortic regurgitation	2	1	2			1	100.0	51.6					
Total Average	17	15	14	3		11	73.3	22.8	4	26.6	1	2	1
T wave Negativity in Combined Derivations I, II, and III and Aberration of the QRS Complex in all Derivations													
Hypertension	2	2	2			2	100.0	15.5					
Chronic myocarditis	1	1	1			1	100.0	18.0					
Angina pectoris	1	1	1			1	100.0	9.0					
Aortic	1	1	1			1	100.0	3.0					
Total Average	5	5	5			5	100.0	11.1					
Grand total Grand average	135	113	101	34	3	98	86.7	12.7	12	10.0	3	4	5

TABLE 2—CONTROL SERIES

Clinical Classification	Total Number	Patients Heard From	Sex		Deaths Other Than Cardiac	Cardiac Deaths			Patients Living					
			Males	Females		Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse	
T wave Negativity in Derivation I and Aberration of the Q R S Complex in all Derivations														
Hypertension	35	26	17	18	3	8	30.7	28.5	15	57.6	3	11	1	
Chronic myocarditis	22	14	17	5	1	4	28.5	18.0	9	64.2	3	5	1	
Arteriosclerosis	2	2	2	2					2	100.0		1	1	
Angina pectoris	7	5	7			2	40.0	12.0	3	60.0	1	2		
Exophthalmic goiter	1	1	1						1	100.0			1	
Adenoma with hyperthyroidism	4	4	1	3					4	100.0	3	1		
Mitral regurgitation	3	2	4	1		1	50.0	12.0	1	50.0		1		
Double mitral lesion	3	1	2	1		1	100.0	10.0						
Aortic regurgitation	8	5	6	2		2	40.0	48.0	3	60.0	1	1	1	
Total Average	90	60	58	32	4	18	30.0	21.4	38	63.3	11	22	5	
T wave Negativity in Combined Derivation I and II and Aberration of the Q R S Complex in all Derivations														
Hypertension	12	8	8	4	3	3	37.5	6.7	2	25.0		1	1	
Chronic myocarditis	3	3	3		1				2	66.6		1	1	
Arteriosclerosis	2	2	2						2	100.0		2		
Angina pectoris	2	1		2					1	100.0			1	
Mitral regurgitation	3	2	2	1					2	100.0		2		
Aortic regurgitation				1										
Aortic aneurysm	1			1										
Total Average	23	16	15	8	4	3	18.7	6.7	9	36.2		6	3	
T wave Negativity in Combined Derivation II and III and Aberration of the Q R S Complex in all Derivations														
Hypertension	3	3	2	1		2	66.6	7.0	1	33.3		1		
Chronic myocarditis	5	4	4	1		1	25.0	2.0	3	75.6		2	1	
Arteriosclerosis	1	1		1					1	100.0			1	
Angina pectoris	3	3	3		1	1	33.3	18.0	1	33.3	1			
Mitral regurgitation	2	1	1	1	1									
Double mitral lesion	1	1		1					1		1			
Aortic regurgitation	2	2	2						2	100.0	1	1		
Total Average	17	15	12	5	2	4	26.6	13.5	9	60.0	3	4	2	
T wave Negativity in Combined Derivations I, II, and III and Aberration of the Q R S Complex in all Derivations														
Hypertension	2	2	2		2									
Chronic myocarditis	1	1	1						1	100.0		1		
Angina pectoris	1	1	1						1	100.0		1		
Aortic regurgitation	1			1										
Total Average	5	4	4	1	2				2	50.0		2		
Grand total Grand average	135	95	89	46	12	25	26.3	13.9	58	61.0	14	34	10	

were myocardial degeneration associated with hypertension and angina pectoris, each three cases (17.6 per cent), chronic endocardial valvular disease with mitral regurgitation and with aortic regurgitation, each two cases (11.8 per cent), and myocardial degeneration associated with arteriosclerosis and chronic endocardial valvular disease with mitral regurgitation and stenosis, each one case (5.9 per cent)

B Cardiac Mortality—Fifteen patients have been heard from and

TABLE 3—SUMMARY OF THE MORTALITY STATISTICS IN GROUPS 1, 2 AND 3

Clinical Classification	Total Number	Patients Heard From	Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
				Number	Percentage	Average Time Since Examination, Mos.	Number	Percentage	Improved	Unchanged	Worse
T wave negativity in Derivation I	146	115	3	73	63.4	8.5	39	33.9	9	18	12
T wave negativity in combined Derivations I and II	63	49		32	65.3	12.7	17	34.6	4	8	5
T wave negativity in combined Derivations II and III	189	149	9	48	32.2	11.0	92	61.7	33	39	20
T wave negativity in combined Derivations I, II, and III	51	40	3	25	62.5	12.7	12	30.0	2	7	3
Total Average	449	353	15	178	50.4	11.2	160	45.3	58	72	40
Aberration of the Q R S complex in all derivations	112	81	3	51	62.9	14.2	27	33.3	6	15	6
T wave negativity in Derivation I and aberration of the Q R S complex in all derivations	90	73	3	63	86.3	8.4	7	9.5	2	2	3
T wave negativity in combined Derivations I and II and aberration of the Q R S complex in all derivations	23	20		19	95.0	8.5	1	5.0			1
T wave negativity in combined Derivations II and III and aberration of the Q R S complex in all derivations	17	15		11	73.3	22.8	4	26.6	1	2	1
T wave negativity in combined Derivations I, II, and III and aberration of the Q R S complex in all derivations	5	5		5	100.0	11.1					
Total Average	135	110	3	98	86.7	12.7	12	10.6	3	4	5

eleven (73.3 per cent) have died of heart disease in one and nine-tenths years following examination. Four patients (26.6 per cent) are living and one is improved, two are unchanged, and one is worse (Table 1)

Fifteen patients in the control group have been heard from and four (26.6 per cent) have died of heart disease in an average of thirteen and one-half months following examination. Nine patients are living (60 per cent), three are improved, four are unchanged, and two are worse (Table 2)

T WAVE NEGATIVITY IN COMBINED DERIVATIONS I, II, AND III
AND ABERRATION OF THE QRS COMPLEX IN ALL
DERIVATIONS (FIVE CASES)

This group is too small to be of statistical value but is presented to maintain continuity of data

A Clinical Types of Heart Disease—Myocardial degeneration associated with hypertension occurred in two cases (40 per cent) and chronic

TABLE 4—SUMMARY OF THE MORTALITY STATISTICS OF THE CONTROL SERIES
IN GROUPS 1, 2 AND 3

Clinical Classification	Total Number	Patients Heard From	Deaths Other Than Cardiac	Cardiac Deaths			Patients Living				
				Number	Percentage	Average Time Since Examination Mos	Number	Percentage	Improved	Unchanged	Worse
Control Series to											
T wave negativity in Derivation I	116	93	7	26	26.8	28.8	60	64.5	19	28	13
T wave negativity in combined Derivations I and II	63	40	4	7	17.5	10.8	29	72.5	13	11	5
T wave negativity in combined Derivations II and III	189	110	6	22	20.0	18.0	82	74.5	36	33	13
T wave negativity in combined Derivations I, II, and III	51	39	3	8	20.5	19.2	28	71.7	10	17	1
Total Average	449	282	20	63	22.3	19.2	199	70.5	78	89	3
Aberration of the QRS complex in all derivations	112	65	6	14	21.5	13.7	45	69.0	14	28	3
T wave negativity in Derivation I and aberration of the QRS complex in all derivations	90	60	4	18	30.0	21.4	38	63.3	11	22	5
T wave negativity in combined Derivations I and II and aberration of the QRS complex in all derivations	23	16	4	3	18.7	6.7	9	56.2	0	6	3
T wave negativity in combined Derivations II and III and aberration of the QRS complex in all derivations	17	15	2	4	26.6	13.5	9	60.0	3	4	2
T wave negativity in combined Derivations I, II, and III and aberration of the QRS complex in all derivations	5	4	2				2	50.0		2	
Total Average	135	95	12	25	26.3	13.9	58	61.0	14	31	10

myocarditis, angina pectoris, and chronic endocardial valvular disease with aortic regurgitation, each one case (20 per cent)

B Cardiac Mortality—All patients have been traced and all have died of heart disease (100 per cent), in an average of eleven and one-tenth months following examination (Table 1)

Four patients in the control series have been heard from and no cardiac deaths are recorded. Two patients are alive and report their condition unchanged (Table 2)

The high and early cardiac mortality attending significant T wave negativity associated with aberration of the Q R S complex in all derivations is apparent. The association of these electrocardiographic abnormalities is an index of marked myocardial involvement and is attended by the greatest mortality in the three studies.

SUMMARY

The cardiac mortality attending significant T wave negativity and aberration of the Q R S complex in all derivations in order of importance as revealed in this study was

T wave negativity in combined Derivations I, II and III and aberration of the Q R S complex in all derivations, 86.7 per cent in 12.7 months. Control series, 0.

T wave negativity in combined Derivations I and II and aberration of the Q R S complex in all derivations, 95.0 per cent in 8.5 months. Control series, 18.7 per cent in 6.7 months.

T wave negativity alone in Derivation I and aberration of the Q R S complex in all derivations, 86.3 per cent in 8.4 months. Control series, 30.0 per cent in 21.4 months.

T wave negativity in combined Derivations II and III and aberration of the Q R S complex in all derivations, 73.3 per cent in 22.8 months. Control series, 26.6 per cent in 13.5 months.

Total of group, 86.7 per cent in 12.7 months. Control series, 26.3 per cent in 13.9 months.

Tables 3 and 4 have been constructed to summarize the mortality statistics of the three groups. From the standpoint of prognosis the electrocardiographic abnormalities rank in order of importance as follows: (1) significant T wave negativity associated with aberration of the Q R S complex in all derivations of the electrocardiogram (group cardiac mortality 86.7 per cent in twelve and seven-tenths months), (2) aberration of the Q R S complex in all derivations of the electrocardiogram (group cardiac mortality 62.9 per cent in fourteen and two-tenths months), and (3) significant T wave negativity (group cardiac mortality 50.4 per cent in eleven and two-tenths months).

These statistics, I hope, will help to allay the scepticism of some cardiologists regarding the significance of the electrocardiographic disorders under discussion. The recognition of these graphic changes alone, I believe, justifies the use of the electrocardiograph as a most valuable and important clinical adjunct.

CLINICAL STUDIES OF QUINIDIN

II ALTERATIONS IN THE CARDIAC MECHANISM AFTER ADMINISTRATION OF QUINIDIN TO PATIENTS WITH AURICULAR FIBRILLATION WITH CONSIDERATION OF CERTAIN TOXIC EFFECTS OF THE DRUG *

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During the past four years, sufficient evidence has been accumulated to indicate that in a certain number of patients suffering from fibrillation of the auricles (about 50 per cent), oral administration of quinidin sulphate serves to restore the normal cardiac rhythm. The circumstances which determine the issue are not yet altogether clear. A summary of the earlier literature, together with a preliminary report dealing with the treatment of four cases in the Hospital of the Rockefeller Institute, has already appeared ¹.

The results of experiments done in this Hospital to determine the pharmacologic action of this drug have likewise been reported ². It is the purpose of the present communication to record in detail the alterations in the mechanism of the heart's action which have been observed in the first eleven patients to whom quinidin has been administered ³. A more detailed report of the experimental studies will appear shortly. A discussion of the clinical aspects of quinidin therapy is reserved for a subsequent paper in which a larger material will be considered ⁴.

MATERIAL AND METHOD

Five hundred and seven electrocardiograms, taken of eleven patients, have been measured and analyzed. The cases represent an unselected material. They have been under observation prior to treatment for periods ranging from one month to one and a half years, and are known to have been fibrillating for at least these periods of time.

* From the Hospital of the Rockefeller Institute for Medical Research.

* Presented in abstract before the New York Academy of Medicine, Nov 17, 1921.

1 Levy, R. L. Restoration of the Normal Cardiac Mechanism in Auricular Fibrillation by Quinidin, Preliminary Report, *J. A. M. A.* **76** 1289 (May 7) 1921.

2 Cohn, A. E., and Levy, R. L. Experimental Studies of the Pharmacology of Quinidin, *Proc. Soc. Exper. Biol. & M.* **18** 283, 1921. Experiments with Quinidin on Conduction and on the Refractory Period in the Dog's Heart *Proc. Soc. Exper. Biol. & M.* **19** 174, 1922.

3 A preliminary account of this study was published in the *Proc. Soc. Exper. Biol. & M.* **19** 88, 1921.

4 In this paper will be considered the symptoms attendant on administration of the drug, the duration of its action, the effects of altered rhythm on vital capacity and heart size as determined teleroentgenographically, the relationship between digitalis and quinidin therapy, etc.

After a preliminary dose of from 0.2 to 0.4 gm quinidin to test for the presence of an idiosyncrasy to members of the cinchona group, 0.4 gm of the drug has been given by mouth, in gelatin capsules, either three times daily or every two hours, until the establishment of normal rhythm or the appearance of untoward symptoms indicated cessation of therapy. No more than 2 gm quinidin was administered in twenty-four hours, though treatment has been continued daily for as long as ten days.

Electrocardiograms were taken in some instances as often as every five minutes during the time when a change of rhythm was anticipated. Usually curves were made at one or two hour intervals on the days on which the drug was given and at least once daily throughout the entire period of observation. The usual three limb leads were employed. Records made in this fashion do not always permit of accurate measurement of auricular rate when the auricles are fibrillating. References to rate, therefore, unless otherwise specified, are to be taken as indicating the number of ventricular beats per minute.

RESULTS

The results of this electrocardiographic study are of interest in illustrating the great variety of alterations in the mechanism of the heart's action which may be induced by quinidin. They have, furthermore, a significance for clinical medicine in so far as they indicate the manner in which the transition from fibrillation to normal rhythm may be expected to occur. But of paramount importance is the significance attached to various toxic effects which have been observed, as evidenced by the occurrence of rhythms usually associated with poisoning of the heart muscle. It is particularly desirable that those concerned with the care and treatment of patients with heart disease should be familiar with the signs and dangers of quinidin intoxication.

For the purpose of discussion, the eleven cases naturally fall into two groups: (1) three patients, in whom, on different occasions, the normal mechanism was restored nine times, and who, in all, received twelve courses of quinidin; (2) eight patients, in whom restoration of the normal mechanism was not accomplished and who received, in all, eleven courses of quinidin. Detailed case records are appended.

CASES IN WHICH THE NORMAL RHYTHM WAS RESTORED

Sequence of Events—In order to learn in what sequence the various changes in cardiac mechanism occurred, detailed analyses of all electro-

Courses 2, 3 and 4), the drug caused a reduction in the number of ventricular contractions. Alterations in rate occurred in from one to three hours after beginning treatment. Tachycardia was followed at times by the appearance of premature beats, arising more commonly in the right, but occasionally in the left ventricle. The ectopic ventricular contractions were frequently transitory (Cases 1 and 2), but in one case (Case 3), they were the precursors of paroxysms of ventricular tachycardia, to which particular reference will be made later. If electrocardiograms were taken at sufficiently frequent intervals, the transitional mechanisms in the common order of their appearance were coarser fibrillation, that is to say, waves in the electrocardiogram having a higher voltage and denoting retardation of auricular rate,⁵ impure auricular flutter,⁶ auricular flutter, and finally, normal rhythm (Fig 4). This sequence was not invariably exhibited in all its phases and it is possible that one or more of the intermediate mechanisms may be omitted.

Transition—In one patient the transition from auricular flutter to the normal rhythm was photographed in the second lead (Fig 5). The abruptness of the change is remarkable. The first twelve interauricular intervals in the curve range from 0.2180 to 0.2580 second (Table 2) with maximum variation of 0.04 second. The corresponding phases of successive cycles are strikingly uniform in contour. The maximum variation in interventricular intervals is 0.0240 second.⁷ There follows a period of altering auricular activity, denoted by the next seven P waves, which exhibit increasingly greater deviations from the usual form. The interauricular intervals are, on the whole, longer than in

5 Drury, A. N., and Iliescu, C. C. The Restoration of the Normal Cardiac Mechanism in Cases of Auricular Fibrillation by Means of Quinidin Sulphate, *Brit. M. J.* 7: 511 (Oct. 1) 1921. These authors, by use of direct chest leads, have secured records in which accurate counts of auricular rate were possible and have noted progressive retardation after quinidin.

6 By impure auricular flutter is meant a mechanism in which auricular (P) waves are present, but in which they are somewhat irregularly spaced and of varying contour, in contradistinction to the regularity of interauricular intervals and constancy of form of corresponding P waves in pure flutter. It is to be regarded as intermediate between auricular fibrillation and flutter.

7 Lewis, T., in speaking of the lengths of auricular cycles in auricular flutter, states that "the maximal variation of the cycles in the same curves is usually less, probably considerably less than 0.01 second, probably it may amount to, but does not materially exceed, 0.02 second on occasion. It seems advisable that the term auricular flutter should be confined to disorders, be they clinical or experimental, in which comparable variations in the lengths of auricular cycles are found not to be exceeded." *Heart* 7: 127, 1920. These statements are based on measurements of the curves of seven cases of flutter, in which interventricular, not interauricular intervals were determined. In one of these cases the maximal variation in interventricular intervals was 0.0265 second. A discussion of the validity of Lewis' criteria is not within the scope of this paper. There seems no reason to doubt that the curve shown in Figure 5 is a record of auricular flutter.

TABLE 1—SUMMARY OF CASES IN WHICH THE NORMAL MECHANISM WAS RESTORED

Case and Hosp Nos	Clinical Diagnosis	Quinidin, Gm	Duration of Admin Days	Original Mechanism	Effect on				Mechanisms After Quinidin								Remarks			
					Rate	P R Sec	T	QRS	Coarse Fib	Impur Flutter	Fib + Imp Flutter	Flutter	Normal Rhythm	VPCOR	VPOL	APC		Vent Tachy	S A Block	Aur Tachy
1 3968	Syphilis, chronic myo carditis	4.6	6	Aur Fib, * VPL, VPOL	+ (1)†	0.13-0.15	+ (5)			+ (3)			+ (4)	+ (2)		+ (6)			Patient partly digitalized prior to quinidin administration, APC appeared after onset of normal rhythm. Patient not digitalized, ventricular rate 185 before quinidin administration, APC again appeared after onset of normal rhythm, 6 days after prolongation of QRS was noted it returned to normal duration	
		1.2	1	Aur Fib, VPL	— (2)	0.12-0.14	+ (3)	+ (5)		+ (4)		+ (6)	+ (7)	+ (1)		+ (8)				
		0.4	1	Aur Fib, VPL	— (1)	0.12-0.13	+ (3)						+ (2)			+ (4)				
		0.4	1	Aur Fib, VPL	— (2)	0.12-0.14	+ (4)						+ (3)			+ (6)				
2 4330	Chronic endocarditis, mitral stenosis and insufficiency	1.2	1	Normal rhythm, VPL APC, VPCOR									+ (1)							
		1.6	2	Aur Fib, VPR	+ (1)	0.16	+ (5)						+ (2)		+ (3)	+ (6)			APC and VPCOR disappeared after quinidin	
		0.8	1	Aur Fib, VPR	— (1)	0.14-0.16	+ (3)												T wave changed and APC appeared after onset of normal rhythm, in pure flutter intervened between normal rhythm and reversion to fibrillation	
		0.4	1	Aur Fib, impure flutter, flutter	— (3)	0.16-0.17	+ (5)			+ (1)			+ (4)						APC inconstant	
3 4118	Chronic endocarditis, mitral stenosis and insufficiency	1.2	1	Aur Fib															No significant effect	
		8.4	7	Aur Fib	+ (1)	0.21-0.24	+ (8)			+ (6)	+ (4)		+ (7)	+ (2)	+ (5)	+ (11)	+ (3)	+ (9)	+ (10)	T wave change transient, sino auricular block observed once after onset of normal rhythm one paroxysm of auricular tachycardia after onset of normal rhythm
		6.4	5	Aur Fib	— (2)	0.21	+ (7)			+ (5)	+ (3)		+ (6)	+ (1)	+ (4)					Normal rhythm maintained for less than 24 hours
		1.6	1	Aur Fib	+ (1)						+ (2)			+ (4)	+ (5)		+ (3)			

* Key to abbreviations used in Tables 1 and 2

Aur Fib Auricular fibrillation
 VPCOR Ventricular premature contractions right
 VPL Ventricular premature contractions left
 APC Auricular premature contractions
 † The numbers in the various columns denote the chronological sequence of the changes observed

VPR Ventricular preponderance, right
 VPL Ventricular preponderance, left
 APC Auricular premature contractions

Vent Tachy Ventricular tachycardia
 Aur Tachy Auricular tachycardia
 S-A Block Sino auricular block
 Under rate + = acceleration — = retardation

the group immediately preceding, and range from 0.2280 to 0.2860 second, with maximum variation of 0.0580 second. There is coincidentally gradual widening of the interventricular periods. Then comes a relatively long asystole of both auricles and ventricles and this is followed by prompt resumption of the sinus rhythm.

A consideration of the manner in which the transition occurs is of some interest in relation to the theory that a circus excitation is the nature of the disturbed mechanism at the basis of fibrillation and flutter of the auricles. According to this concept, first clearly defined by A. G. Mayer, working with the umbrella of the jelly fish, developed and demonstrated in heart muscle by Garrey and by Mines, and more recently elaborated and applied to human physiology by Lewis, cessa-

TABLE 2—MEASUREMENT OF ELECTROCARDIOGRAM (LEAD II) SHOWING TRANSITION FROM AURICULAR FLUTTER TO NORMAL RHYTHM *

Cardiac Mechanism	Interauricular Intervals, Second	Interventricular Intervals, Second	P R Time, Second
Auricular flutter	0.2324 0.2510 0.2260 0.2360 0.2180 0.2288 0.2200 0.2230 0.2212 0.2210 0.2580 0.2210	0.4520 0.4760 0.4608 0.4606 0.4530 0.4558	
Altering auricular activity	0.2455 0.2362 0.2280 0.2860 0.2610 0.2420	0.4936 0.5760 0.6310	
Transition	1.0880	1.0349	
Normal rhythm	0.7720 0.8200 0.8450 0.8594	0.7752 0.8256 0.8456 0.8610	0.1696 0.1632 0.1640 0.1620

* Measurements were made with the use of a projection apparatus.

tion of auricular fibrillation or flutter may, on theoretic grounds, be induced in three ways: (1) by lengthening the path of the excitation wave in the auricle, (2) by accelerating the rate of conduction of the impulse through the auricular muscle, (3) by lengthening the refractory period of this muscle. It is clear from the electrocardiogram shown in Figure 5, that immediately before and during the transition the excitation wave is traversing a different path from that travelled during the preceding period of flutter, for the P waves alter in form. They are, moreover, irregularly and more widely spaced. To which of the three conceivable causes just mentioned this change may be ascribed, it is not possible definitely to establish. It is known, however, that in the dog's heart quinidin retards the rate of conduction

of the impulse through the muscle of the auricle and prolongs the refractory period^{2,8} It furthermore raises the threshold of excitability of the auricle, so that a faradic current adequate to induce fibrillation prior to the injection of quinidin does not suffice to cause the arrhythmia after the drug has been given² It is probable that the resultant of these effects determines whether cessation of fibrillation takes place Slowing of the conduction rate may be regarded as exerting an unfavorable or negative effect in arresting the circus movement, whereas the raised threshold of excitability and more particularly, lengthening of the refractory period, exercise a favorable or positive effect in promoting this result The decreased rate of the flutter waves in this instance at all events indicates that probably a longer path, perhaps at a slower rate, was traversed by the excitation wave The alteration in path may have been necessitated by an increase in the refractory period

After the resumption of normal rhythm, the auricular waves, though distinct, showed at times decided variations both in contour and voltage Evidence of such change in the P waves (Fig 5) in Cycles 14 and 39 is striking There is apparently still a tendency for the impulse to be initiated at a point other than at the sinus node or to traverse an unusual and sinuous path in its course through the auricle

Ectopic Beats, Auricular Tachycardia, Sino-Auricular Block — Ectopic auricular contractions were observed in all three cases at times after the normal mechanism was resumed Their occurrence points to the persistent presence of a point of origin away from the sinus node, and probably within the musculature of the auricle Additional evidence strengthening the belief that there is disturbance in both initiation and propagation of the impulse through the auricle in individuals suffering from atrial fibrillation is afforded by Case 3, in which, during the brief period in which normal rhythm was maintained, sino-auricular block and paroxysms of ectopic auricular tachycardia occurred (Fig 6)

When auricular premature beats became numerous, these, as well as ectopic ventricular contractions, could be abolished by the further administration of quinidin (Case 1, fifth course, Fig 3) It is to be noted that the ventricular premature beats disappeared earlier than those arising in the auricle⁹

8 Lewis, T, Drury, A N, Iliescu, C C, and Wedd, A M Observations Relating to the Action of Quinidin on the Dog's Heart, with Special Reference to Its Action on Clinical Fibrillation of the Auricles, Heart 9 55, 1921

9 We have since had occasion to test the effect of quinidin in patients showing no disturbance in rhythm other than ectopic beats arising either in auricles or ventricles In certain of these individuals, the undisturbed normal mechanism can be restored and, if desired, maintained by proper quinidin dosage

Rate—On the day on which normal rhythm was established, the ventricular rate usually ranged from 80 to 90 and on the following day from 60 to 70, subsequently remaining at or about this level during the period in which the sequential rhythm prevailed. When the transition from the normal rhythm to fibrillation or flutter took place, there was correspondingly a gradual acceleration of rate, a level eventually being reached in the course of twenty-four hours at which the ventricles then continued to beat with relatively slight variations.

A-V Conduction—Conduction through the auriculoventricular bundle when the sinus rhythm was present was within normal limits in two cases, as indicated by the P-R time. In the third case the P-R interval was prolonged (0.24 sec.), but it is not possible to say whether this was a drug effect or was due to interference with the passage of the impulse from other causes.

Intra-Ventricular Conduction—In one individual (Case 1, second course), there was definite evidence that quinidin caused interference with the spread of the excitation wave through the ventricles (partial intraventricular block) (Fig. 1). The QRS interval rose from 0.10 sec. before quinidin administration to 0.13 sec. after the drug had been given, and did not return to its former value for five days. There was no coincident prolongation of A-V conduction.

Alteration in Ventricular Complex—In the series of curves just described (Fig. 1) is seen an example of change in the contour and voltage of the ventricular complex after quinidin administration. This is exhibited particularly in the R and S waves and in the altered form and position of the notching. Similar changes were observed in one other case. There is, presumably, some change in the path of the impulse through the ventricles.

T Wave—The T wave was distinctly affected by quinidin, in that it tended to reverse its direction and change its form after the normal rhythm was established.¹ Though slight variations in this portion of the electrocardiogram were among the early effects of quinidin medication, the more striking changes occurred after the sinus rhythm had prevailed for twenty-four hours and were best seen in Lead III (Fig. 2). When the fibrillatory mechanism was resumed, the T wave usually returned to its original direction and form either at once or after a short interval. It is of interest to note that in one instance however, (Case 2, first course), the T wave change preceded the alteration in cardiac mechanism. On the last day of normal rhythm the T wave in Lead III changed from upright to inverted. On the following morning, auricular fibrillation was again recorded the T wave remaining as on the previous day. It is, therefore, clear that, although change in the form of the T wave and change in rhythm often occur synchro-

nously, they are not necessarily interdependent. In dogs in which quinidin was injected similar alterations in the T wave were noted.² These observations are recorded without any attempt at interpretation, since the significance of change in this portion of the electrocardiogram is by no means clear.

Influence of Digitalis—Digitalization prior to quinidinization was not essential for success in restoring the normal mechanism. For in the same individual (Case 1), the normal rhythm was on one occasion restored after digitalis administration, with ventricular rate ranging from 90 to 100 (first course), and at another time, after no digitalis was given, when the ventricles were beating at the rate of 180 per minute (second course). A number of observations bearing on this point have been made and will be discussed more fully at another time.

Effect of Atropin—Intravenous injection of atropin sulphate (from 1.0 to 1.5 mgm.) in these patients at a time when fibrillation was present and again when the normal rhythm prevailed, resulted in the usual increase in ventricular rate, but in no noteworthy alteration in the cardiac mechanism or in the form of the electrocardiogram.

CASES IN WHICH RESTORATION OF THE NORMAL MECHANISM WAS NOT ACCOMPLISHED

In this group of eight patients, evidences of the undesirable action of quinidin were more frequently observed (Table 3).

Tachycardia—As in the cases in which it was possible to establish normal rhythm, tachycardia was commonly the first effect noted and was often sufficiently troublesome to cause complaint. Having once been initiated, it was rarely prolonged beyond four or five hours after the drug was discontinued. In one patient (Case 10, first course), in whom simple tachycardia was induced by quinidin, definite signs and symptoms of heart failure ensued. There was palpitation, dyspnea, epigastric distress, large tender liver, accumulation of invisible edema, as evidenced by gain in weight and oliguria and a striking rise in venous pressure from 10.8 to 20.2 cm. of water.¹⁰ A graphic account of these findings is given in Figure 9. A course of digitalis therapy was followed by prompt disappearance of symptoms and signs of decompensation.

Coarse Fibrillation, Impure Flutter, Flutter—Coarsening of fibrillatory waves, indicating retardation of auricular rate, was noted on five occasions. It was at times among the earliest detected changes in the electrocardiogram, but in other instances was seen as a later

¹⁰ Observations of venous pressure were made by the method of Hooker. *Am J Physiol* 35:73, 1914.

TABLE 3—SUMMARY OF CASES IN WHICH RESTORATION OF THE NORMAL RHYTHM WAS NOT ACCOMPLISHED

Case and Hosp No.	Clinical Diagnosis	Quinidin Gm	Duration of Admin Days	Original Mechanism	Effect on			Mechanisms After Quinidin						Remarks				
					Rate	P R	T	QRS	Coarse Fib	Impure Flutter	Fib Imp Flutter	Flutter	Normal Rhythm		VPCB	VPL	APC	Vent Tachy
4 3083	Chronic endocarditis, mitral stenosis and insufficiency aortic insufficiency	18	5	Aur Fib VPR	+ (1)													
5 4274	Chronic endocarditis mitral stenosis and insufficiency aortic insufficiency	16	7	Aur Fib VPR VPCI	+ (1)					+ (1)		+ (5)	+ (6)		+ (2)	+ (3)		
6 4127	Chronic endocarditis, mitral stenosis and insufficiency	36	5	Aur Fib VPR, VPCB (occasional)	+ (1)										+ (2)	+ (4)		Patient digitalized before beginning quinidin therapy, VPCB increased in number, at times resulting in coupled rhythm
7 4227	Chronic myocarditis	32	5	Aur Fib VPL	+ (3)							+ (10)	+ (5)		+ (1)	+ (3)		After digitalis, fibrillatory mechanism returned
8 4345	Chronic endocarditis, mitral stenosis and insufficiency	62	8	Aur Fib	+ (1)		+ (3)			+ (6)	+ (4)				+ (5)	+ (2)		
9 4308	Chronic endocarditis, mitral stenosis and insufficiency	24	3	Aur Fib	+ (1)		+ (4)			+ (1)	+ (5)	+ (6)				+ (2)		
10 4349	Chronic endocarditis, mitral stenosis and insufficiency aortic insufficiency	30	4	Aur Fib	+ (1)		+ (3)								+ (2)			Patient digitalized prior to quinidin administration
		16	3	Aur Fib	+ (3)		+ (4)			+ (1)					+ (2)			Patient again digitalized before beginning quinidin
		40	5	Aur Fib	+ (1)		+ (2)											Quinidin and digitalis combined
11 4267	Chronic myocarditis	88	10	Aur Fib VPL	+ (2)					+ (3)						+ (1)		Patient digitalized before beginning quinidin therapy

effect The mechanism by which slowing is produced is not precisely to be ascertained It is known, however, that one of the pharmacologic actions of quinidin is to depress conductivity in the auricle, and it is conceivable, and altogether likely, that slowed auricular rate is an exhibition of this effect When still greater depression of conduction has been produced, impure flutter occurs This was observed on three occasions in combination with periods of fibrillation and twice as the dominant rhythm In two patients (Cases 5 and 7) impure flutter was followed by flutter, but larger dosage was not effective in restoring the normal rhythm In Case 5, the flutter was of short duration, lasting but twenty minutes, after which a mixed rhythm with periods of fibrillation and impure flutter was recorded In Case 7, however, flutter persisted for three days and was followed, after administration of digitalis, by reversion to the fibrillatory rhythm

These observations serve to demonstrate the close interrelationship between fibrillation, impure flutter and flutter, and lend support to the concept that they are all dependent upon the same basic disturbance, namely, a circus contraction in the auricle In these respects, Lewis' experimental data¹¹ are confirmed for the clinic

Ventricular Premature Beats—Of the greatest significance to the clinician are those arrhythmias which indicate irritation of the ventricular muscle Reference has already been made, in discussing the first group of cases, to the occurrence of ectopic ventricular premature beats, which arose more often in the right, but occasionally in the left ventricle These were observed in all of the eight cases in the series now under discussion In some instances they were transitory, disappearing spontaneously or after more of the drug was given They assume particular importance in those individuals in whom occasional ventricular premature beats are not present prior to the beginning of treatment They may occur as isolated extrasystoles, or, in such fashion as to cause coupled rhythm, like that seen in the early stages of digitalis poisoning (Case 6, first course, Fig 7)

Paroxysms of Ventricular Tachycardia—If more quinidin is given, however, ventricular premature beats may occur in rapid succession in a manner to result in paroxysms of ectopic ventricular tachycardia (Cases 3, 6, 7 and 11, Figs 6 and 8), or as a continuous sequence of extrasystoles arising in an ectopic focus in the ventricle (Case 7, Fig 8) Case 7 is of particular interest in this connection, in that ventricular tachycardia occurred at first during the fibrillatory period, then at a time when auricular flutter with 3:1 block was present and subsequently, with slower auricular rate and 2:1 block The

¹¹ Lewis T Observations upon Flutter and Fibrillation Part IV Impure Flutter, Theory of Circus Movement, Heart 7 293, 1920

paroxysms in the three cases in which this mechanism was seen were fortunately of short duration, lasting always less than twenty hours and sometimes disappearing in the course of three hours after the last dose of quinidin was given

Ventricular tachycardia assumes a real significance if it is borne in mind that in dogs injected with digitalis or strophanthin this irregularity is not infrequently the precursor of ventricular fibrillation and death. Dogs which have received quinidin occasionally, though rarely, die with this arrhythmia.² Several sudden and unexplained deaths are reported by careful observers following quinidin administration in patients in whom, at necropsy, dilatation of the heart but no evidence of pulmonary or other embolism was found. It is quite possible that in these patients ventricular fibrillation was the cause of death. Unfortunately the cardiac mechanism shortly before and at the time of death has not been recorded.

In certain individuals, then, quinidin is a highly toxic substance for heart muscle, even in doses ordinarily regarded as safe in clinical therapeutics. Until further details of its action are known, it is wise to insist that patients receiving this drug should remain in bed, preferably in a hospital, under close observation by nurse and physician. Where possible therapy should be controlled by graphic records. Physicians who prescribe quinidin should do so with the realization that in proper hands it possesses great therapeutic virtue, whereas unintelligently given, it may cause disastrous effects and fall into undeserved disrepute.

SUMMARY

1 An electrocardiographic study has been made of eleven patients with auricular fibrillation who received quinidin sulphate by mouth. In three, to whom quinidin was given on twelve occasions, the normal rhythm was restored nine times. In eight, to whom the drug was given on eleven occasions, restoration of the normal rhythm was not accomplished.

2 In the cases in which normal rhythm was established, the first effect noted was usually acceleration of ventricular rate, next in order came ectopic ventricular beats. The transitional mechanisms in the common order of appearance were coarser fibrillation, denoting retardation of auricular rate, impure flutter, flutter and normal rhythm.

3 The transition from flutter to normal rhythm has been photographed in the second lead and has been described.

4 The occurrence of variations in the form of P waves, ectopic auricular contractions, auricular tachycardia and sino-auricular block after resumption of the sinus rhythm, is adduced as evidence that there is, even at this time, a tendency for the impulse to be initiated at a point other than at the sinus node and to traverse an unusual path in its course through the auricle.

5 Both auricular and ventricular premature beats could, on occasion, be abolished by further exhibition of the drug

6 The effects on rate, A-V conduction, intraventricular conduction and on the T wave have been discussed

7 Reference has been made to the influence of digitalis on the issue of quinidin administration and to the effect of atropin after establishment of the sinus rhythm

8 In the cases in which restoration of the normal mechanism was not accomplished, evidences of the undesirable action of quinidin were more frequently observed. Tachycardia was troublesome and in one instance was followed by signs and symptoms of heart failure

9 The close interrelationship of fibrillation, impure flutter and flutter was evident in that rapid change from one of these mechanisms to the other was frequently seen. This observation lends support to the concept that they are all dependent on the same basic disturbance, namely, a circus contraction in the auricles

10 Ectopic ventricular beats were seen after quinidin in all of the eight cases under discussion. These occurred at times in such fashion as to cause coupled rhythm

11 After the continued administration of quinidin, paroxysms of ectopic ventricular tachycardia sometimes ensued. This arrhythmia is significant for the clinician, for in dogs injected with digitalis or strophanthin it is not infrequently the precursor of ventricular fibrillation and death. In the three cases in which this mechanism was seen, the paroxysms were fortunately of short duration

12 In certain patients, quinidin is a toxic substance for heart muscle, even in doses ordinarily regarded as safe for clinical use. Carefully administered, the drug possesses great therapeutic virtue, whereas unintelligently given, it may be expected to cause undesirable effects

APPENDIX

REPORT OF CASES

CASES IN WHICH THE NORMAL MECHANISM WAS RESTORED

CASE 1—Hosp No 3968 Male, aged 55 Diagnosis Syphilis, chronic myocarditis. Known duration of fibrillation, one and a half years, duration of cardiac symptoms, two years

This patient received quinidin sulphate on five different occasions, four times to restore the normal rhythm, the fifth time in an attempt to abolish auricular and ventricular premature beats at a time when the sinus rhythm prevailed

First Course—March 10 to 15 4.5 gm were given in six days. The patient had been taking 0.1 gm digitalis (digitan) daily prior to quinidin administration. The original mechanism, as recorded electrocardiographically, was fine auricular fibrillation. There was left ventricular preponderance and an occasional left ventricular premature beat

First Day 0.2 gm at 3 and 6 p m. There was no evident effect

Second Day 0.2 gm at 7 9 11 a m and 1 and 3 p m. At 10 50 a m after 0.8 gm, the ventricular rate rose from 110 to 142 and right ventricular

premature contractions appeared, these were transient and were not again observed during this course of treatment. By 4 p. m. the rate had again fallen to 95.

Third and Fourth Days. No quinidin given.

Fifth Day. 0.4 gm. at 12 noon, 4 and 8 p. m. Again there was acceleration of rate, which at 6 p. m. was 130.

Sixth Day. At 6 a. m., the ventricular rate was 140, with but 114 beats palpable at the wrist. 0.4 gm. at 8 and 10 a. m., 12 noon, 2, 15 and 4 p. m. At 2:50 p. m., after 1.6 gm., there was impure flutter with ventricular rate of 115. This was followed after another 0.4 gm., by restoration of the normal mechanism with rate of 80. The sinus rhythm was recorded one hour and fifty-five minutes after the onset of flutter. On the following day the T wave in Lead III, which

Case 1 Hosp No 3968

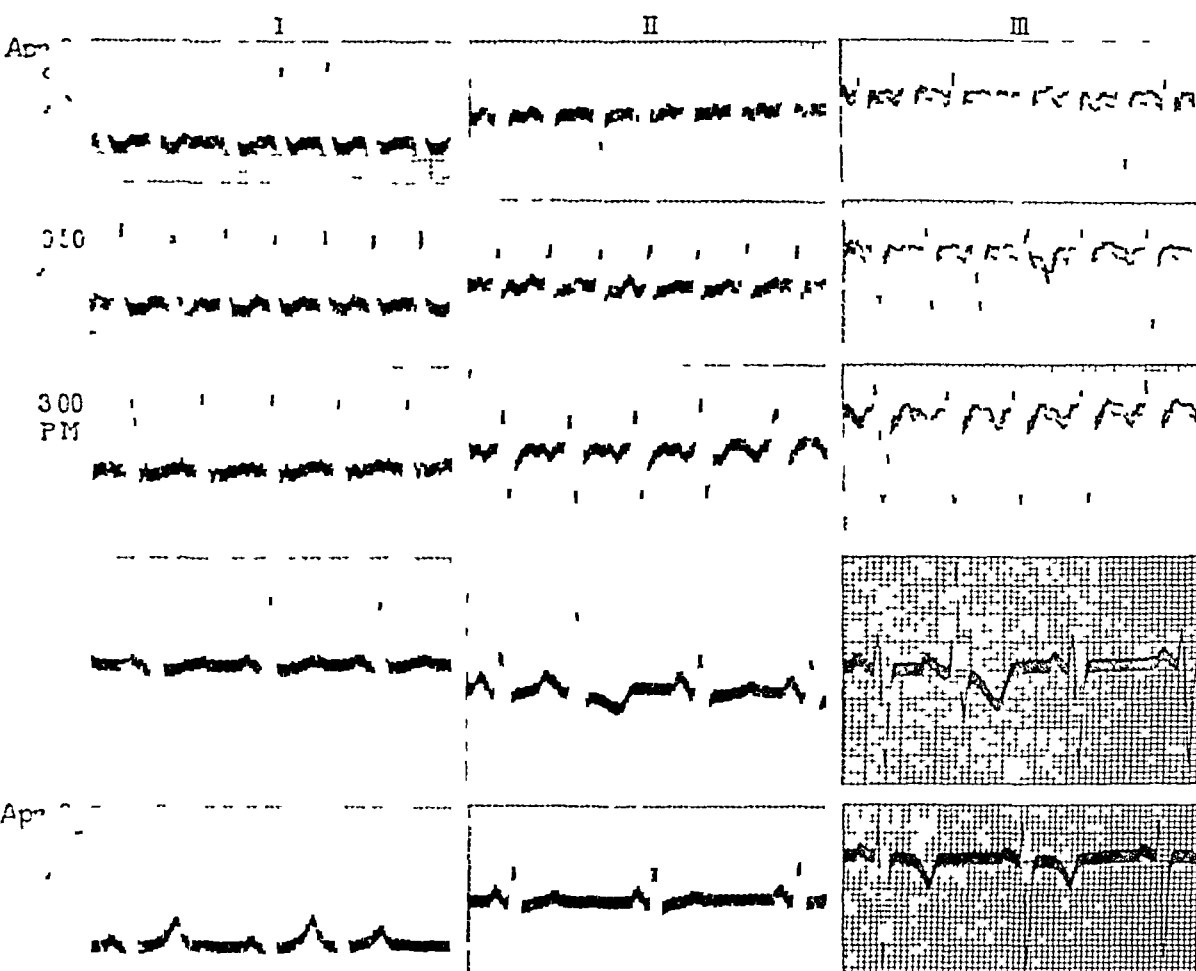


Fig 1—Case 1 Hosp No 3968 April 13 Quinidin sulphate, 0.4 gm., at 10:30 a. m., 12 noon, and 2:30 p. m.

9:10 a. m., control. Auricular fibrillation, ventricular rate, 185, QRS = 0.10 sec.

10:50 a. m., after 0.4 gm. Auricular fibrillation, ventricular rate, 185, right ventricular premature contraction (Lead III).

3:00 p. m., thirty minutes after 1.2 gm. Auricular flutter, auricular rate, 280, ventricular rate, 140. QRS = 0.13 sec.

3:30 p. m., one hour after 1.2 gm. Normal rhythm, ventricular rate, 95, P-R = 0.13 sec. QRS = 0.13 sec.

April 18, five days later. 9:15 a. m. Normal rhythm, auricular premature contractions, ventricular rate, 60, P-R = 0.13 sec, QRS = 0.10 sec.

had been upright, became inverted and auricular premature beats were present. The latter disappeared spontaneously after being present for four days. The P-R (conduction) time during the period of normal rhythm ranged from 0.13 to 0.16 second. The sinus rhythm prevailed for twenty-three days. On the twenty-fourth day fine auricular fibrillation with ventricular rate of from 120 to 135 suddenly reappeared. In the course of three days the T wave in all three leads assumed the opposite direction from that previously recorded. There were occasional left ventricular premature beats. On the twenty-fifth day the ventricular rate rose to 184 and remained at this level until quinidin was again administered five days later.

Second Course—April 13. Three doses of 0.4 gm each were given at two hour intervals. After 0.4 gm, right ventricular premature contractions appeared, but were transitory. After 0.8 gm there was gradual fall in rate from 180 to

Case 1 Hosp No 3968

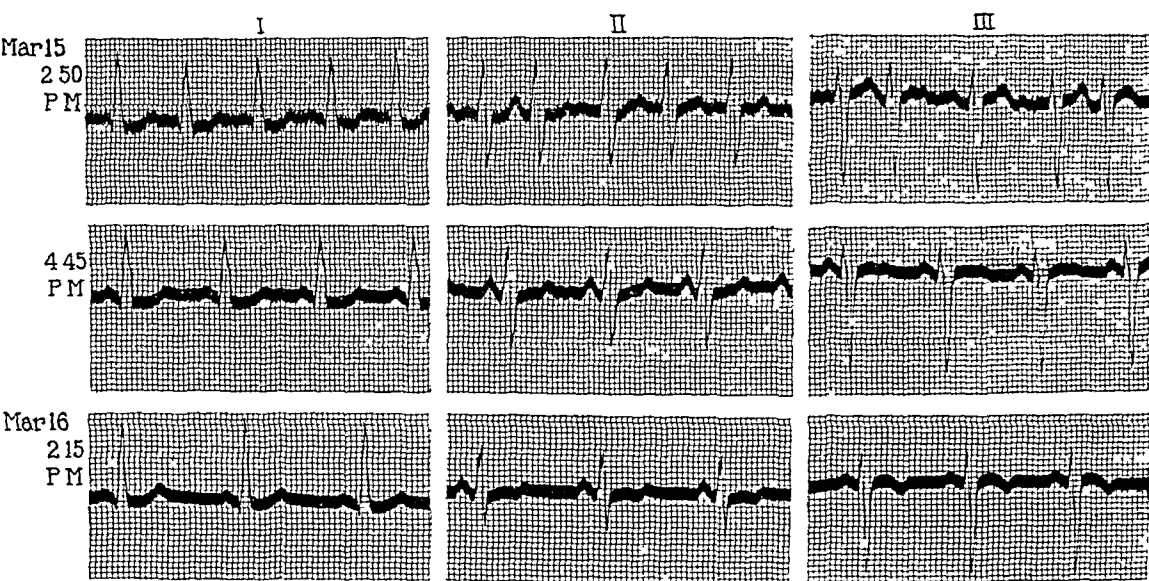


Fig 2—Case 1 Hosp No 3968 March 15 Quinidin sulphate, 0.4 gm, at 8 and 10 a m, 12 noon, 2 15 and 4 p m

2 50 p m, after 1.6 gm Auricular fibrillation, ventricular rate 115, T wave = $\mp + +$

4 45 p m, forty-five minutes after 2 gm Normal rhythm, ventricular rate 80, P-R = 0.15 sec, T wave = $+ + +$

March 16, twenty-one hours later 2 15 p m Normal rhythm, ventricular rate 69, P-R = 0.14 sec, T wave = $+ \mp -$

140 The T wave in Lead I changed from inverted to upright. Three hours after beginning treatment and one hour after the second dose, there was impure flutter with ventricular rate of 145. The QRS interval was 0.10 second. Impure flutter persisted for forty minutes after which 2:1 flutter was recorded. The QRS interval was now from 0.12 to 0.13 second. After forty-five minutes of flutter, normal rhythm with rate of 95 was established. The T wave in Lead III changed at once from upright to inverted. Auricular and right ventricular premature beats were present, the latter disappearing in the course of a few hours. The QRS interval still ranged from 0.12 to 0.13 second. Next day the rate was 69 and was maintained at about 70, until fibrillation reappeared twenty-one days after onset of normal rhythm. QRS group remained wider than normal, i e, more than 0.10 second, for six days, then resumed its former value of 0.10 second. On the twenty-first day of normal rhythm fibrillation

with ventricular rate of 120 set in. Next day there was further acceleration of rate, from 170 to 180, and the T wave in Lead III changed from inverted to upright.

Third Course—May 6 0.4 gm sufficed to restore normal rhythm on this occasion, the ventricular rate falling rapidly from 185 to 94, and on the following day to 72. The T wave in Lead III again changed from upright to inverted and auricular premature beats appeared. Normal rhythm was present for only four days, then for a day fibrillation supervened, for a few hours there was spontaneous resumption of normal rhythm and then again reversion to fibrillation with ventricular rate of 180. After the onset of fibrillation the T wave in Lead III again became upright. While the sinus rhythm prevailed, P-R (conduction) time was from 0.12 to 0.13 second.

Case 1 Hosp No 3968

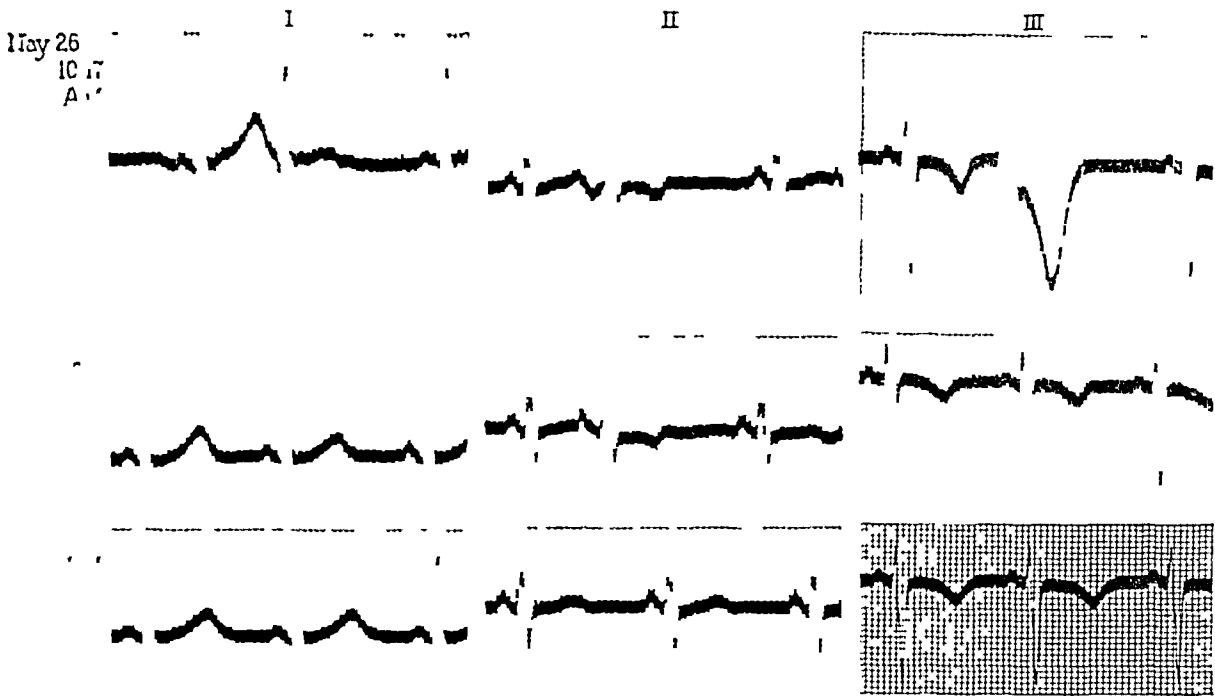


Fig 3—Case 1 Hosp No 3968 May 26 Quinidin sulphate, 0.4 gm, at 8 and 11 a. m., and 1 p. m.

10:17 a. m., after 0.4 gm. Normal rhythm, auricular and right ventricular premature contractions, rate 75, P-R=0.13 sec.

12:14 p. m., after 0.8 gm. Normal rhythm, auricular premature contractions, rate 66, P-R=0.14 sec.

2:15 p. m., after 1.2 gm. Normal rhythm, rate 61, P-R=0.12 sec.

Fourth Course—May 18. After seven days of fibrillatory mechanism, 0.4 gm was again given, and 2:1 flutter ensued forty minutes after quinidin was taken with no demonstrated intermediate mechanism. When flutter first appeared, the ventricular rate was 180 but fell in the course of thirty-five minutes to 145. One hour and two minutes after the onset of flutter there was a normal rhythm at the rate of 108. There were occasional auricular premature beats. The T wave in Lead III changed from upright to inverted. At the end of four hours the ventricular rate had fallen to 75. P-R (conduction) time was from 0.12 to 0.14 second. Three days after the establishment of normal rhythm auricular flutter reappeared but the fibrillatory mechanism was not resumed. On the following day one dose of 0.4 gm sufficed once more to restore the normal mechanism though occasional auricular premature beats were present.

Fifth Course—May 26 In the course of four days many premature contractions, both of auricular and right ventricular origin, were present. These were sufficiently numerous to cause complaint, 12 gm, given in three doses of 04 gm each, at three hour intervals sufficed entirely to abolish the ectopic contractions. The normal rhythm has now been maintained in this patient for more than eleven months. He has been taking 04 gm quinidin every second day, and three doses of 04 gm each on one day every two weeks. At times premature beats of auricular origin have been present, but the larger dosage has usually served to restore the undisturbed normal mechanism.

CASE 2—Hosp No 4330 Male, aged 26 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency. Known duration of fibrillation, one month, duration of cardiac symptoms, eight years.

Case 2 Hosp No 4330

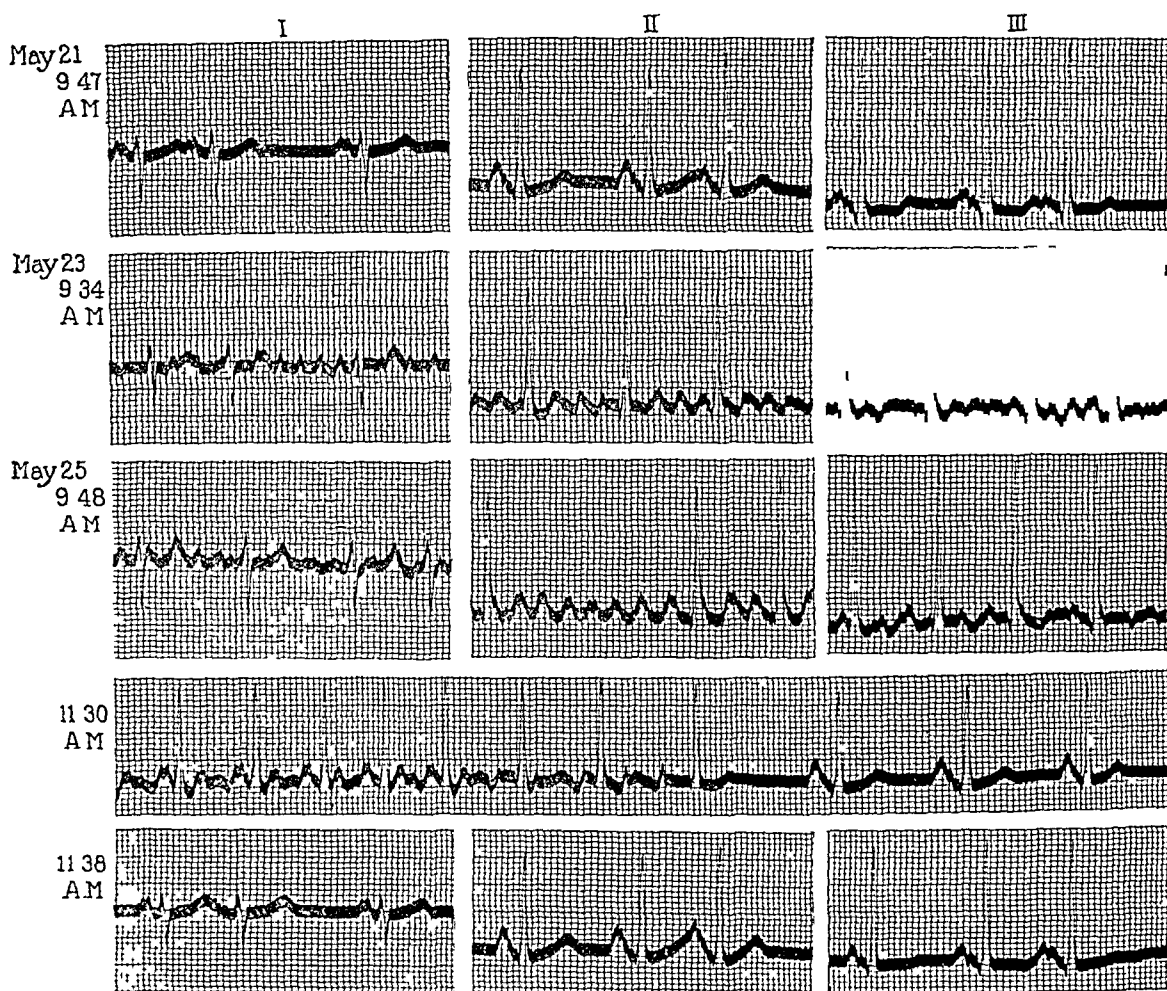


Fig 4—Case 2 Hosp No 4330 Normal rhythm had prevailed for eighteen days after a previous course of quinidin. May 21 9 47 a m Normal rhythm still present, rate 80, P-R=0.15 sec.

May 23 9 34 a m Auricular fibrillation and impure flutter, ventricular rate 92.

May 25 9 48 a m, control Impure flutter and flutter, ventricular rate 90. 10 05 a m, quinidin sulphate, 04 gm.

11 30 a m, eighty-five minutes after 04 gm. Lead II Transition from auricular flutter, with ventricular rate of 122 and auricular rate of 244, to normal rhythm, with ventricular rate of 72, P-R=0.16 sec.

11 38 a m Normal rhythm, ventricular rate 86, P-R=0.16 sec.

This patient received three courses of quinidin, each time with restoration of normal rhythm. He was kept in bed in the hospital for one month without medication before beginning quinidin administration. The original mechanism was coarse auricular fibrillation, there was right ventricular preponderance. Ventricular rate prior to treatment ranged from 100 to 110.

First Course—March 17 and 18 1.6 gm given in two days.

First Day 0.2 gm, at 11 30 a m and 1 30 p m. The first effect noted was an increase in the rate of the ventricles to 125, even after this small preliminary dose. At 4 30 p m, three hours after the second dose, there was auricular flutter with 3:1 block.

Second Day 0.4 gm at 7, 9 and 11 a m. At 9 30 a m, thirty minutes after the second dose, the rate was 140, and the mechanism auricular flutter with 3:1 block. There were a few left ventricular premature beats. One hour and five minutes after 1.2 gm had been given, normal rhythm was established with a rate of 95. Premature beats were no longer present. The T wave in Lead III, which, prior to treatment, had been inverted, became upright in the course of two hours. There was a progressive fall in rate and at the end of five hours the ventricles were beating 73 times per minute. P-R (conduction) time was from 0.16 to 0.17 second. There were occasional auricular premature beats. The normal rhythm was maintained for thirteen days. It is of interest to note that on the last day of normal rhythm the T wave in Lead III again changed from upright to inverted, and the following morning auricular fibrillation was recorded once again, the T wave remaining as on the previous day. Ventricular rate was 110. Two days later there was impure flutter with rate of 130, followed by coarse fibrillation with rate ranging from 110 to 115.

Second Course—April 7. On the eighth day after reversion to fibrillation 0.4 gm was given at 7 and 9 a m. The normal rhythm was again promptly reestablished at 9 30, the intermediate mechanisms, if such were present, not being recorded. The ventricular rate was 85. The T wave in Lead III again changed from inverted to upright, and auricular premature beats were present. These were observed to disappear and reappear at times. P-R (conduction) time was from 0.14 to 0.16 second. On this occasion the normal rhythm persisted for twenty-three days, the ventricular rate ranging from 66 to 80. On the twenty-third day there was again auricular fibrillation with a ventricular rate of 120 and the T wave in Lead III became inverted. Four days later the normal rhythm was resumed without medication, and persisted for twenty days, the P-R (conduction) time being from 0.15 to 0.16 second and the T wave in Lead III being upright. Again there were occasional auricular premature beats. On the twentieth day there was a mixture of auricular flutter and fibrillation, with ventricular rate of 92 and an inverted T wave in Lead III. On the following day there were seen in the same curve both impure flutter and auricular fibrillation, and on the day after this flutter, impure flutter and auricular fibrillation.

Third Course—May 25 0.4 gm was given at 10 05 a m. At 11 o'clock there was impure flutter and at 11 30, one hour and twenty-five minutes after quinidin had been given, the transition from auricular flutter to the normal mechanism was recorded in Lead II. There were occasional auricular premature beats. T_a was again upright. There was a fall in ventricular rate from 122 during the period of flutter, to 72 after the sinus rhythm was restored. The P-R (conduction) time ranged from 0.16 to 0.17 second.

The patient was discharged from the hospital three days later with a normal rhythm, but did not report for observation as directed. He returned for examination four months later showing the fibrillatory mechanism with a ventricular rate of 96. Three doses, of 0.4 gm each, again restored the normal mechanism, and this was maintained for three months with the intermittent quinidin medication given on a plan similar in its essentials to that outlined for Case 1.

CASE 3—Male, aged 55. Diagnosis. Chronic endocarditis (rheumatic), mitral stenosis and insufficiency. Known duration of fibrillation, fifteen months, duration of cardiac symptoms, six years.

Case 2. Hosp No 4330

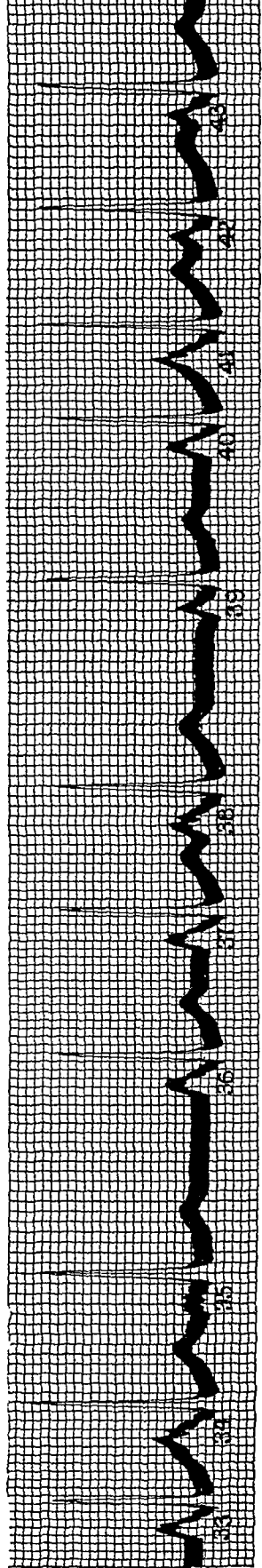
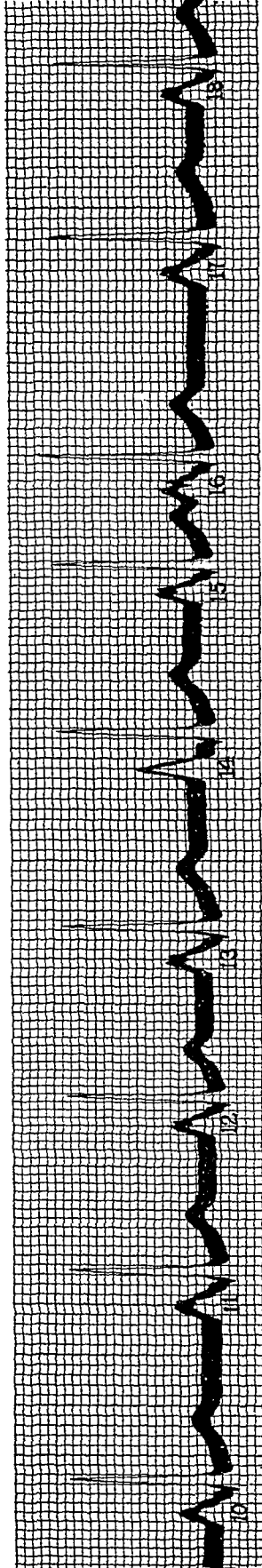
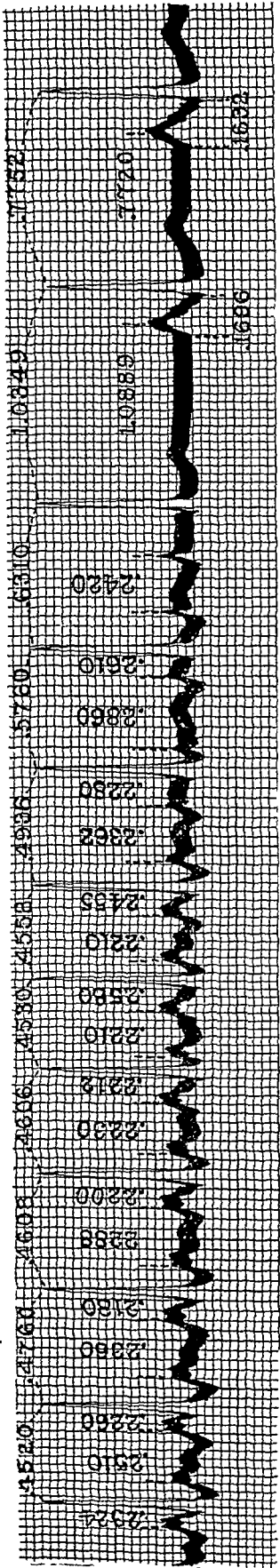


Fig 5—Case 2 Hosp No 4330 Transition from auricular flutter to normal rhythm (Lead II) with tenth to eighteenth, and thirty-third to forty-third cycles after establishment of sinus rhythm Occasional auricular premature contractions (For tabulation of measurements, see Table 2)

The patient was partly digitalized prior to quinidin therapy, having taken some digitalis, the amount of which was not definitely known, before entering the hospital. He received four courses of quinidin. On two occasions only was the normal rhythm reestablished. The original mechanism was coarse auricular fibrillation, with a ventricular rate of 145.

First Course—May 13. 12 gm. was given in one day. The patient received 0.4 gm. at 10 30 a. m., 12 30 and 2 30 p. m. There was no significant effect.

Second Course—May 19 to 25. 8.4 gm. were given in seven days. This course was given six days after the first attempt at therapy.

First Day. 0.4 gm. was administered at 10 a. m., 12 noon, 2 and 4 p. m. The ventricular rate before the first dose was 125, somewhat higher than when the first course was given. After 0.8 gm. this had risen to 150. After 1.2 gm. it was again 120 and there were premature beats of right ventricular origin. At 4 35 p. m., i. e., thirty-five minutes after a total of 1.6 gm. had been administered, there was ectopic right ventricular tachycardia with a rate of 120.

Case 3 Hosp No 4118

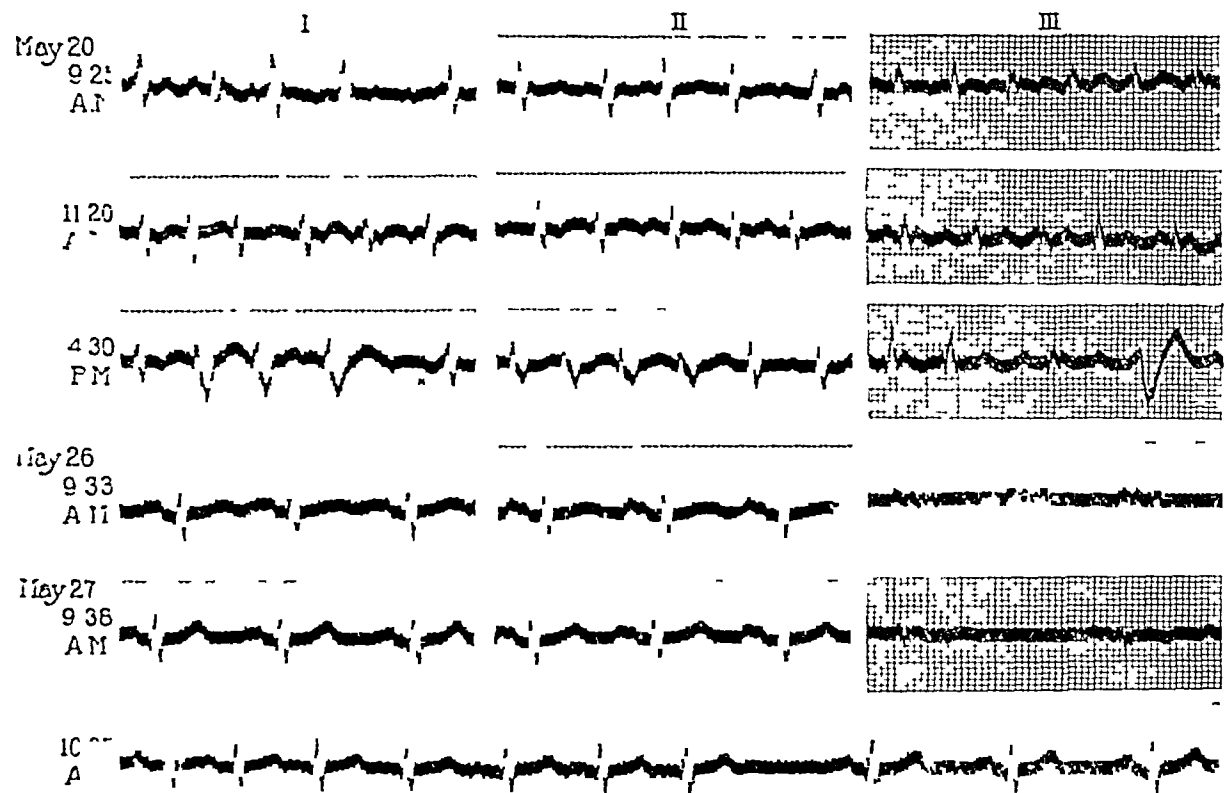


Fig 6—Case 3 Hosp No 4118 May 20 Quinidin sulphate, 0.4 gm., at 10 a. m., 12 noon, 2 and 4 p. m.
 9 25 a. m., control. Auricular fibrillation, ventricular rate 120
 11 20 a. m., after 0.4 gm. Coarser auricular fibrillation, ventricular rate 130
 4 30 p. m., after 1.6 gm. Auricular fibrillation, paroxysms of ventricular tachycardia, isolated left ventricular premature beats
 May 21 and 22 No quinidin given
 May 23 and 24 Quinidin sulphate, 1.6 gm., on each day
 May 25 Quinidin sulphate, 2 gm.
 May 26 9 33 a. m. Normal rhythm, ventricular rate 78, P-R=0.24 sec
 May 27 9 38 a. m. Normal rhythm, sino-auricular block, ventricular rate 80, P-R=0.22 sec
 10 05 a. m. Paroxysm of auricular tachycardia with transition to normal rhythm

Second Day The following morning ventricular tachycardia had disappeared and the ventricular rate was 120. Four-tenths gram was again given at 10 a m, 12 noon, 2 and 4 p m. At 11 20, one hour and twenty minutes after the first dose, there was impure flutter in addition to the coarse fibrillation. At 1 30, one hour and thirty minutes after the second dose, there was again auricular fibrillation without flutter, but there were right ventricular premature beats. The ventricular rate was 140. At 4 30, thirty minutes after the fourth dose, there were paroxysms of ventricular tachycardia originating first in the right ventricle, then in the left, together with isolated left ventricular premature beats, the rate was 130.

Third Day There was again auricular fibrillation with a ventricular rate of 126. No drug was given on this day or on the fourth day of treatment.

Fifth Day 0.4 gm was given at 11 a m, 1, 3 and 5 p m. The ventricular rate at 9 54 a m, before giving quinidin, was 145, at 4 15 p m it was 115. No change in mechanism was noted.

Sixth Day At 9 27 a m, there was impure flutter with rate of 130, 0.4 gm was given at 10 a m, 12 noon, 2 and 4 p m. At 1 30 p m, one hour and thirty minutes after a total of 0.8 gm, had been given, there were right ventricular premature beats. At 3 55 p m, fifty-five minutes after the third dose, there were paroxysms of left ventricular tachycardia with a rate of 130. At 4 15 p m these had disappeared and there were isolated right ventricular premature beats.

Seventh Day 0.4 gm given at 9 30 and 11 30 a m, 1 30, 3 30 and 6 p m. Electrocardiograms taken on this day showed impure flutter with a ventricular rate ranging from 110 to 130. At about 7 p m the normal rhythm was established, the patient being distinctly conscious of the alteration in mechanism. The following morning at 9 33, this was recorded with a rate of 78, the P-R (conduction) time being 0.24 second. The normal rhythm persisted for fourteen days, during which the rate ranged from 75 to 90, and the P-R (conduction) time from 0.21 to 0.24 second. On the second day of normal rhythm an isolated instance of sino-auricular block was photographed, and later on this same day a short paroxysm of auricular tachycardia with the transition to the normal rhythm. On the twelfth and thirteenth days of normal rhythm there were auricular premature beats, and on the fourteenth day auricular fibrillation with rate of 102 was again present. The T wave during the time when normal rhythm was present showed no significant alteration. Fibrillation proceeded for three days, the ventricular rate during most of this period ranging from 150 to 160.

Third Course—June 16 to 20 **First Day** 0.4 gm given at 10 30 a m, 12 30 and 2 30 p m. At 11 30 a m, one hour after the first dose, there were right ventricular premature beats. At 1 40, one hour and ten minutes after the second dose, there were portions of the curves showing impure flutter in addition to fibrillation, with both right and left premature beats, the ventricular rate being 140. The ventricular premature beats disappeared before the third dose was given but were again present one hour after 1.2 gm had been administered.

Second Day Impure flutter with coarse fibrillation still prevailed, 0.4 gm given at 10 a m, 12 noon and 2 p m. At 10 50, fifty minutes after the first dose, the curves showed flutter and impure flutter with a ventricular rate of 160. After the second dose there was again coarse fibrillation with right ventricular premature beats. One hour after the third dose there was again coarse fibrillation with impure flutter and right ventricular premature beats.

Third Day No quinidin was given. The mechanism was impure flutter with rate of 145.

Fourth Day No records were made.

Fifth Day At 9 50 there was coarse fibrillation and impure flutter with a rate of 160, 0.4 gm given at 11 a m, 1, 3, 5 and 7 p m. The rate remained at about this level. At 3 40, forty minutes after the third dose, there were occasional premature beats arising in both right and left ventricles. Fifty minutes later these were more numerous.

Sixth day A record taken at 9 50 a m showed the normal mechanism with a rate of 88, the P-R (conduction) time 0.21 second and an upright T wave in Lead III, it having been previously inverted At 4 p m on this day the rate was 85 and there were occasional auricular premature beats The duration of normal rhythm was brief, and on the following morning there was again coarse auricular fibrillation with rate of 150 and flattening of the T wave in Lead III

Fourth Course June 22 1.6 gm were given in one day, 0.4 gm at 10 30 a m, 12 30, 2 30 and 4 30 p m At 11 30, one hour after administering 0.4 gm, there was, in addition to auricular fibrillation, impure flutter with rate of 180 One hour after the second dose, the rate had fallen to 142, and at 3 36, one hour and six minutes after the third dose, the rate was 125 There were at this time paroxysms of right and left ventricular tachycardia At 4 25 these paroxysms were no longer noted, nor was impure flutter present There was coarse auricular fibrillation with isolated right and left premature beats, the ventricular rate being 138

On the following morning the ventricular rate was 134, and the patient complained of palpitation and dyspnea He was accordingly given digitalis in the form of digitan, 1 gm on this day and 0.5 gm the following morning No further attempt at quinidin therapy was undertaken

CASES IN WHICH THE RESTORATION OF THE NORMAL MECHANISM WAS NOT ACCOMPLISHED

CASE 4—Female, aged 32 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency, aortic insufficiency Known duration of fibrillation, five months, duration of cardiac symptoms, two years

In five days 4.8 gm was given The original mechanism was auricular fibrillation with right ventricular preponderance The patient was well digitalized before beginning quinidin treatment, the ventricular rate ranging from 70 to 80

First Day Feb 28 0.2 gm given at 11 50 a m and 5 30 p m There was no notable effect

Second Day 0.4 gm given at 12 30 and 6 p m There was a sharp rise in heart rate to 142 at 8 p m with a gradual return to the former level of 64 the following morning

Third Day 0.4 gm was given at 9 50 a m, 2 and 6 p m Again there was a sharp rise in rate, reaching its maximum of 135 at 8 p m, with return to 75 by the following morning There were, in addition, occasional right ventricular premature beats which were first recorded three hours after the first dose on this day, and persisted throughout the night The following morning the rate was 75

Fourth Day 0.4 gm was given at 7 30 and 11 45 a m, and 5 p m The rate again rose to 127 at 6 p m with gradual fall during the night Right ventricular premature beats persisted

Fifth Day The rate in the morning was 82, 0.4 gm was given at 8 and 11 30 a m, and 5 p m Tachycardia again ensued, with maximum rate of 125 at 8 p m Premature beats became more numerous No more quinidin was administered The following morning the rate was again 69 to 74

CASE 5—Male, aged 19 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency, aortic insufficiency Known duration of fibrillation, two months, duration of cardiac symptoms, eight years The original mechanism was fine auricular fibrillation with right ventricular preponderance, the rate ranging from 63 to 80 During seven days 4.2 gm was given

First Day Feb 3 0.1 gm was given at 12 noon and 5 p m No effect was noted

Second Day 0.2 gm given at 11 30 a m and 5 p m The rate remained 70 There was no significant change

Third Day 0.2 gm at 10 a m and 4 p m There was a slight increase in heart rate to 104

Fourth Day The rate had returned to 60 but there were occasional right ventricular premature beats No quinidin was given on this day

Fifth Day 0.4 gm was given at 10 30 a m and 4 p m Three hours after the first dose, the rate was 110, the fibrillatory waves were slightly coarser and there were ectopic beats originating in both left and right ventricles The T wave was unchanged At 8 p m the ventricular rate was 126 but by the following morning it had fallen to 73

Sixth Day The fibrillatory waves were fairly coarse and the premature beats had disappeared, 0.4 gm was given at 10 15 a m, 1 and 4 55 p m At 11 35, one hour and twenty minutes after the first dose, the rate had risen to 91 and there were occasional right ventricular premature beats The T wave in Lead III, which was upright, showed a higher voltage than before At 12 20 the rate was 130, the curve showing auricular fibrillation and impure flutter, and more numerous right and left ventricular premature beats At 4 25, three hours and twenty-five minutes after the second dose, the rate was 128, the rhythm flutter, and premature beats were present as before At 4 45 there was again auricular fibrillation and impure flutter with a rate of 122, and at 5 55 reversion to coarse fibrillation with showers of right and left ventricular premature beats

Case 6 Hosp No 4127

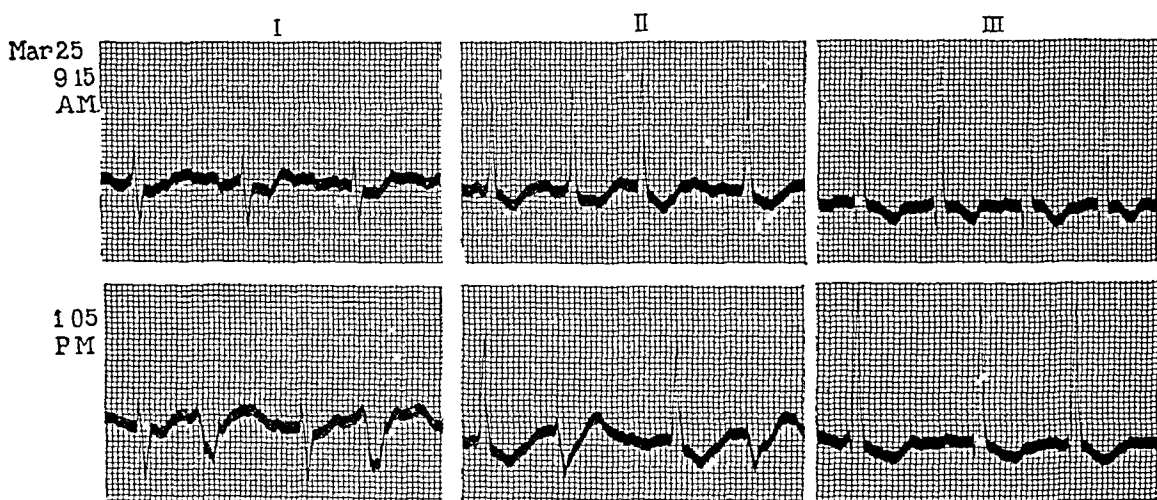


Fig 7—Case 6 Hosp No 4127 March 25 Quinidin sulphate, 0.4 gm, at 7, 9 and 11 a m

9 15 a m, after 0.8 gm Auricular fibrillation, ventricular rate 78

1 05 p m, after 1.2 gm Auricular fibrillation, ventricular premature contractions (Leads I and II), coupled with the usual ventricular complexes, ventricular rate 90

Seventh Day The ventricular rate at 9 30 a m was 70 There was coarse fibrillation with occasional right and left ventricular premature beats, 0.4 gm was given at 11 30 a m, 1 30 and 3 30 p m There was a gradual increase in rate which at 6 p m was 111, but without alteration in mechanism Coarse fibrillation and right and left ventricular premature beats persisted On the following day, the tachycardia was still present, the ventricles beating at the rate of 131 at noon There was also a sharp rise in temperature, which at 4 p m was 102 F Whether or not this febrile reaction bore any relation to quinidin therapy it was not possible to say At the time at which it occurred the patient complained of severe pain in the precordial region and in the left chest The following morning the temperature was again normal, the ventricular rate 74 No more quinidin was administered

CASE 6—Female, aged 23 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency Known duration of fibrillation, thirteen months, duration of cardiac symptoms, five years The patient received two courses of quinidin

First Course—Feb 24 to 28 3.6 gm was given in five days The original mechanism was fine auricular fibrillation with right ventricular preponderance and occasional right ventricular premature beats The rate ranged from 60 to 80 The patient had been receiving digitalis in the form of digitan for a number of days prior to quinidin therapy

First Day 0.2 gm was given at 12 and 2 p m There was no notable effect

Second Day 0.4 gm was given at 7, 9 and 11 a m, and 1 10 p m Two hours and five minutes after the first dose there were numerous right ventricular premature beats which were rhythmically coupled with normal complexes Fifty minutes after the fourth dose the extrasystoles disappeared and were not again recorded for two days There was a slight increase in rate, from 78 to 90

Third Day The rate was again 74 There were no premature beats No quinidin was given on this day

Fourth Day No quinidin was given

Fifth Day The rate at 9 o'clock was 62, 0.4 gm was administered at 9 20 and 11 a m, 1 and 3 p m At noon, one hour after the second dose, the ventricular rate was 94 and remained at a fairly constant level, between 80 and 90, thirty minutes after the fourth dose At this time there were paroxysms of ventricular tachycardia with a rate of 115, and right ventricular premature beats of various forms The paroxysms were still present at 5 45, and at this time left ventricular premature beats as well as others originating in the right ventricle were noted By the following morning the ventricular rate was again 62 and the original mechanism, namely, fine auricular fibrillation, was present No quinidin was given for eight days

Second Course—April 4 to 6 3.2 gm was given in three days

First Day 0.4 gm was given at 11 a m and 4 p m At 3 15 the rate had risen to 145 and right ventricular premature beats were again present

Second Day 0.4 gm was given at 7 15 and 11 15 a m and 4 p m The rate remained at a fairly constant level between 80 and 90, but at 4 15 right ventricular premature beats, which earlier in the day had not been present, reappeared

Third Day 0.4 gm was given at 7 15 and 11 20 a m and 4 p m The rate at 8 a m rose to 117, fell gradually to 87 at 6 p m, but on the following morning was again relatively high, namely from 115 to 125 After a lapse of twenty-four hours, however, the ventricles were beating 73 times per minute No more quinidin was given

CASE 7—Male, aged 58 Diagnosis Chronic myocarditis Known duration of fibrillation, one month, duration of cardiac symptoms, two years This patient received 3.2 gm quinidin in five days The original mechanism was fine auricular fibrillation with left ventricular preponderance He had been in the hospital prior to quinidin therapy for one month, during which time he received no medication The ventricular rate during this time was quite labile, ranging from 90 to 120

First Day March 28 The rate at 9 45 a m was 120, 0.2 gm was given at 10 a m and 12 noon At 2 15 p m there were right and left ventricular premature beats, which by 4 20 had disappeared

Second Day The rate at 9 14 was 112, 0.4 gm was given at 10 a m, 12 and 2 p m At noon the rate had risen to 140 and there were paroxysms of left ventricular tachycardia with isolated left ventricular premature beats These paroxysms persisted throughout the day, becoming longer, so that at 5 30 they were almost continuous

Third Day No quinidin was given The record at 9 25 a m showed 3 1 auricular flutter At 10 40 the curve showed both auricular flutter and fibrillation At 12 10 there was again pure flutter, with an occasional left ventricular premature beat, the ventricular rate ranging from 115 to 120

Fourth Day 3 1 flutter, with ventricular rate of 125, was still present at 9 07 a m, 0.4 gm was given at 10 30 a m and 2 p m At 11 38 there was once again auricular fibrillation and flutter, and at 1 15, 2 1 flutter with ventricular rate of 145 This mechanism persisted throughout the day until

4 o'clock, at which time there was 2 1 flutter, with paroxysms of left ventricular tachycardia

Fifth Day At 9 05 a m the curve showed both impure flutter and fibrillation, 0.4 gm was given at 10 10 a m and 2 p m At 11 30, one hour and twenty minutes after the first dose, there was 3 1 flutter with ventricular rate of 112 At 4 10, two hours and ten minutes after the second dose, there was 2 1 flutter with paroxysms of left ventricular tachycardia, ventricular rate being 132 A record made at 5 05 showed the persistence of this mechanism On the following morning the flutter was still present, the ventricular rate being 120 Digitalis, in the form of digitan, 0.5 gm, was given at 10 a m and again at 11 a m At 11 o'clock there was auricular flutter and fibrillation, with a ventricular rate of 122 On the day following the administration of digitan, the ventricular rate was 80, and fine fibrillation, as it had appeared before beginning quinidin treatment, was again the prevailing mechanism

CASE 8—Male, aged 34 **Diagnosis** Chronic endocarditis (rheumatic), mitral stenosis and insufficiency Known duration of fibrillation, three weeks, duration of cardiac symptoms, one and one-half years The original mechanism

Case 7 Hosp No 4327

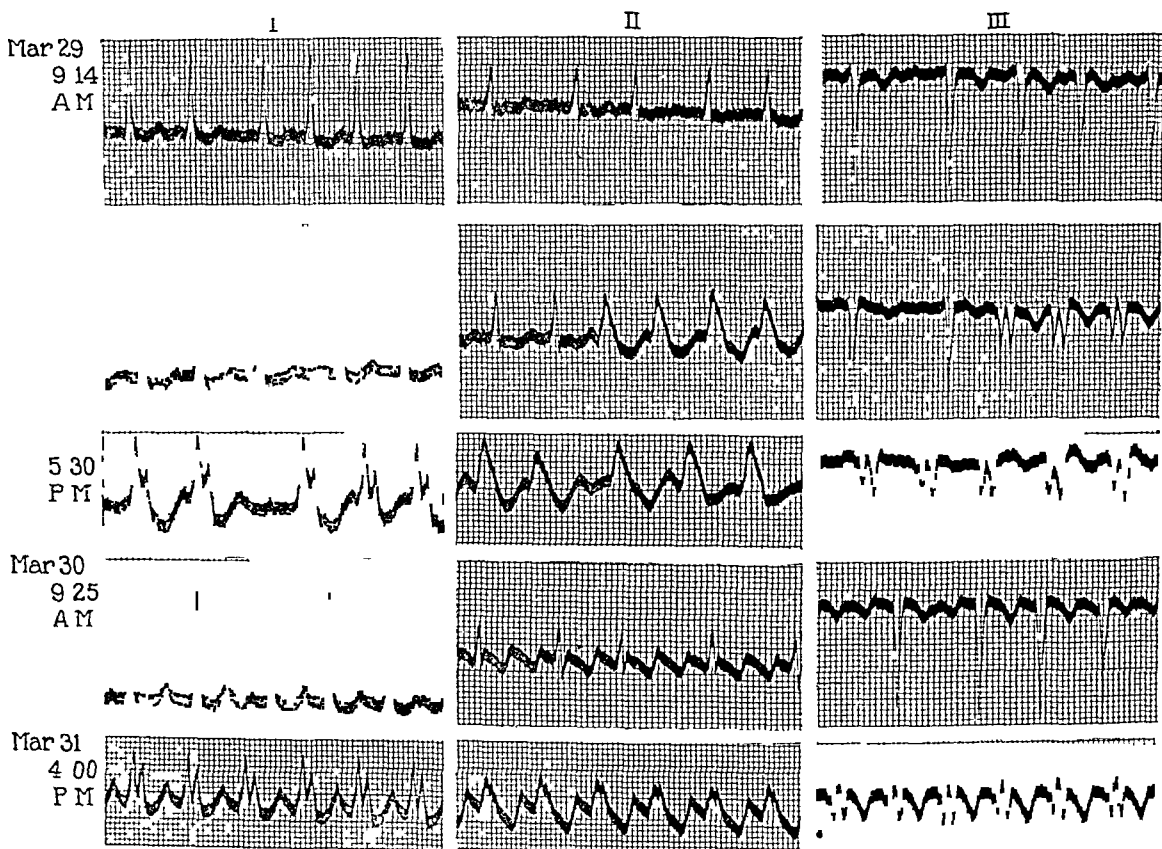


Fig 8 Case 7 Hosp No 4327 March 29 Quinidin sulphate, 0.4 gm, at 10 a m, 12 noon and 2 p m

9 14 a m, control Auricular fibrillation, ventricular rate 112

12 15 p m, after 0.8 gm Auricular fibrillation, paroxysms of left ventricular tachycardia

5 30 p m, after 12 gm Same as 12 noon Longer paroxysms of tachycardia

March 30 No quinidin given

9 25 a m Auricular flutter, ventricular rate 115, auricular rate 345

March 31 Quinidin sulphate, 0.4 gm, at 10 30 a m and 2 p m

4 00 p m, after 12 gm Auricular flutter, paroxysms of left ventricular tachycardia, ventricular rate 135, auricular rate 270

was fine auricular fibrillation. The patient had been in the hospital two weeks prior to quinidin therapy without medication, during which time the ventricular rate ranged from 90 to 110, 62 gm quinidin was administered during an eight day period.

First Day March 30 0.2 gm given at 2 and 4 p m, with rise of ventricular rate from 94 to 105.

Second Day At 9 26 a m the rate was 104 and there were occasional left ventricular premature beats, 0.4 gm was given at 10 15 a m, 12 noon and 2 p m. At 11 30 the fibrillatory waves had become somewhat coarser and the rate was 110, at 2 05 the rate was 135. At 4 15 p m there was impure flutter with a ventricular rate of 120.

Third Day At 9 16 a m the record showed coarse fibrillation and impure flutter with a ventricular rate of 112. The T wave in Lead II, which had previously been upright or diphasic, was now iso-electric, 0.4 gm was given at 10 25 a m, 12 noon and 2 p m. At 11 52 there was impure flutter with right ventricular premature beats, and this persisted throughout the day, the ventricular rate ranging from 90 to 120. The T waves in Leads II and III were variable.

Fourth Day At 9 42 the ventricular rate was 90 and there was coarse auricular fibrillation. The T wave in Lead III, which had before been inverted, was now upright. Only one dose of quinidin, 0.4 gm, was given at 10 a m because of complaint by the patient of epigastric discomfort.

Fifth Day No quinidin was given.

Sixth Day The ventricular rate was 120, 0.4 gm was given at 7 30 and 11 45 a m, and 5 p m. There was no significant change in mechanism but the rate fell gradually to 90 at 3 35 p m. The T wave in Lead III again was variable in its direction.

Seventh Day The ventricular rate was 115, the records showing coarse fibrillation, 0.2 gm was given at 10 10 a m, 2, 4, 6 and 8 p m. This smaller and more fractionated dosage produced no notable effects.

Eighth Day The ventricular rate was 120. There was coarse fibrillation, 0.4 gm was given at 10 15 a m and 12 noon. There was no alteration in mechanism. Headache, slight nausea, sweating and palpitation induced discontinuation of therapy.

CASE 9—Female, aged 33 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency. Known duration of fibrillation, two months, duration of cardiac symptoms, seven years.

This patient received 2.4 gm quinidin in three days. The original mechanism was moderately coarse auricular fibrillation with occasional left ventricular premature beats. The ventricular rate prior to therapy ranged from 95 to 140.

First Day March 31 0.2 gm was given at 11 30 a m and 12 30 p m. There was no noteworthy effect.

Second Day The rate at 9 a m was 112. No ventricular premature beats were recorded, 0.4 gm was given at 10 20 a m, 12 noon and 2 p m. At 12 o'clock the rate had risen to 130 and there were numerous left ventricular premature beats. At 2 45 impure flutter was present, with a ventricular rate of 170. At 4 45 there was impure flutter and coarse fibrillation, with a ventricular rate of 110.

Third Day The ventricular rate at 9 12 a m was 155, with occasional left ventricular premature beats, 0.4 gm was given at 10 a m and 12 noon. There was no alteration in mechanism. The patient complained of severe headache and of precordial pain. On the following day digitalin, 0.5 gm, was given at 11 30 a m and again at 12 30 p m. Twenty-four hours later the ventricular rate was 62. Electrocardiograms showed a finer fibrillation than had previously been noted at any time.

CASE 10—Female, aged 46 Diagnosis Chronic endocarditis (rheumatic), mitral stenosis and insufficiency, aortic insufficiency. Known duration of fibrillation, three weeks, duration of cardiac symptoms, four months. The original mechanism was fine auricular fibrillation. This patient received three courses of quinidin. Prior to the first course her heart had been brought fairly well under the influence of digitalis, the ventricular rate ranging from 78 to 100.

First Course—April 5 to 8 Three gm was given in four days

First Day The ventricular rate at 9 45 was 90, 0.2 gm was given at 12 and 3 p m At 4 55 the ventricular rate was 110 and there were right ventricular premature beats

Second Day 0.2 gm was given at 7 30 a m, 12 noon and 4 30 p m There was no noteworthy change in rate or mechanism

Third Day 0.4 gm was given at 7 30 and 11 30 a m At 9 19 ventricular rate was 110 and the T wave in Lead I, which had previously been upright, was inverted, at 4 25, the rate was 120

Fourth Day The ventricular rate at 9 08 a m was 100, 0.4 gm was given at 10 35 a m, 12 30 and 2 45 p m There was a sharp rise in heart rate to 140 at 2 10 p m, with gradual fall after 4 p m to 84 the following morning The patient at this time was distinctly uncomfortable She was dyspneic, the liver was large and tender, there was epigastric discomfort, and there had been,

Case 10 Hosp No 4349

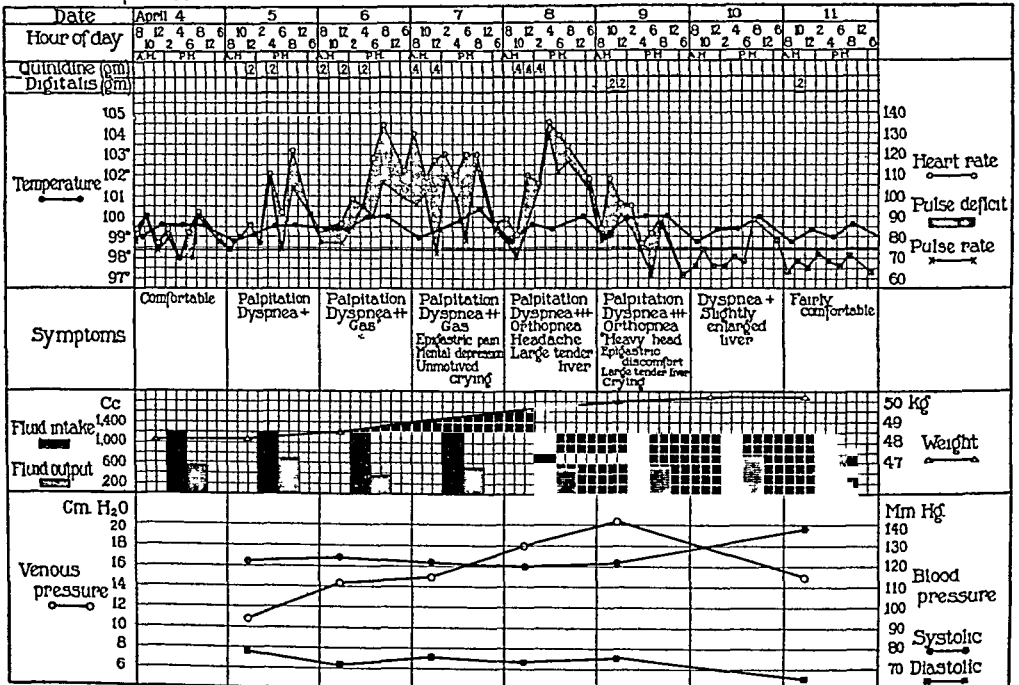


Fig 9—Case 10 Simple tachycardia induced by quinidin was followed by signs and symptoms of heart failure Digitalis afforded prompt relief

during the ten days preceding, a gradual gain in weight Therefore during the next two days she was given a course of digitalis therapy with prompt disappearance of symptoms and improvement in signs The heart rate fell to about 70 and there was no pulse deficit Small doses of digitalis were continued thereafter for sixteen days

Second Course—April 27 to 29 On the seventeenth day after the first course was completed, the second course began, 1.6 gm was given during a three day period

First Day The ventricular rate ranged from 60 to 70, 0.2 gm was given at 12 25 and 2 p m There was no noteworthy effect

Second Day No quinidin was given

Third Day The ventricular rate was 55, 0.4 gm was given at 10 30 a m, 2 30 and 4 30 p m At 4 p m there were occasional right ventricular premature beats At 6 p m the rate had risen to 132, but fell gradually during the night to its former level of 60 to 70 For three days no more quinidin was administered

Third Course—May 2 to 6 Four grams was given during a five day period, and at the same time the patient received 0.1 gm digitan each day

First Day The ventricular rate was 54 The mechanism was fine fibrillation as before, 0.4 gm was given at 10 a m, 12 noon and 2 p m Once again there was a sharp rise in the ventricular rate to 132 at 4 p m, with gradual subsidence of the tachycardia and resumption of a rate of 50 the following morning

Second Day No quinidin was given

Third Day 0.2 gm was given at 10 a m, 12 noon and 2 and 4 p m No significant effect in mechanism or rate ensued

Fourth Day The ventricular rate was 62, 0.2 gm was given at 10 30 a m, 12 30, 2 30, 4 30 and 6 30 p m Again, there was no change in rate or mechanism The T wave in Lead I, which previously had been upright, was now iso-electric

Fifth Day The ventricular rate was 62, 0.2 gm was given at 10 30 a m, 12 30, 2 30, 4 30 and 6 30 p m As before this greater fractionation of dosage caused no effect on rate or mechanism

CASE 11—Male, aged 55 Diagnosis Chronic myocarditis Known duration of fibrillation, seven months, duration of cardiac symptoms, one and one-half years The patient was well digitalized before beginning therapy He received two courses of quinidin His ventricular rate prior to quinidin administration ranged from 66 to 75 The original mechanism was fine auricular fibrillation with left ventricular preponderance

First Course—June 1 to 3 3.2 gm was given in three days

First Day 0.2 gm was given at 1 40 and 3 40 p m There was no demonstrable effect

Second Day 0.4 gm was given at 11 a m, 1 and 3 p m There was no significant effect

Third Day 0.4 gm was given at 10 a m 12 noon, 2 and 4 p m There was a slight rise in the ventricular rate, from 80 to 108 at 6 p m No drug was given during the next two days

Second Course—June 6 to 10 6.8 gm was given in five days

First Day 0.4 gm was given at 10 a m, 12 noon, 2 and 4 p m There was a slight rise in ventricular rate, from 74 to 94

Second Day 0.4 gm was given at 10 a m, 12 noon, 2 and 4 p m The ventricular rate rose from 82 at 9 50 a m to 105 at 3 p m, and there were a number of left ventricular premature beats At 4 30 p m, thirty minutes after the fourth dose, there were paroxysms of left ventricular tachycardia in addition to coarser fibrillatory waves in the remainder of the electrocardiograms and a number of isolated left ventricular premature beats

Third Day Paroxysms of ventricular tachycardia were not present in the morning The ventricular rate was 88, 0.4 gm was given at 9 30 and 11 30 a m, 1 30 and 3 30 p m At 12 33, one hour and three minutes after the second dose, there were again paroxysms of left ventricular tachycardia with a rate of 100, and isolated left ventricular premature beats The same mechanism was again present at 4 30 p m with a rate of 92

Fourth Day Paroxysms of tachycardia no longer were present There were occasional left ventricular premature beats The ventricular rate was 82, 0.4 gm was given at 11 a m, 1, 3 and 5 p m There was a distinct rise in the ventricular rate, which at 8 p m was 128 Left ventricular premature beats persisted

Fifth Day The ventricular rate was 104, 0.4 gm was given at 11 20 a m At 2 p m the ventricular rate was 118 and the patient was decidedly uncomfortable He complained of palpitation, some precordial pain, heaviness of his head and of vague epigastric discomfort His temperature at this time rose to 101 F At 2 15, therefore, digitalis therapy was begun, with prompt reduction in rate to 69 the following day, with subsidence of fever and relief of symptoms

A STUDY OF THE ERYTHROCYTE CURVE AT VARIOUS AGES AND ITS RELATIONSHIP TO HEMOGLOBIN CURVE

LAURENCE HAMPSON MAYERS, A M, M D

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Numerous studies made on the blood of new-born infants have fairly well established the fact that the number of their erythrocytes per cubic millimeter is much higher than it is in the adult. Furthermore, a review of the results of hemoglobin determinations in new-born infants shows a much higher hemoglobin content than is found in adult life. The high hemoglobin content rapidly falls.

Williamson, in a spectrophotometric analysis of 919 cases, shows in his tables that the hemoglobin of the new-born infant averages 23.2 gm hemoglobin per hundred cc of blood. The hemoglobin falls rapidly and by the end of the second month the reading is 18.3 gm. At the end of the fifth month it is 13.7 gm, and then remains practically constant during the next few months, falling to 12.5 gm at the end of the first year. From this point up to the sixth year there is a steady ascent, when it approximates the height of adult life.

Several factors, singly or in combination, may be the cause of this fall, i. e., a sufficient decrease in the number of corpuscles or a decrease in the hemoglobin or a combination of both phenomena. For a study of the problem it was necessary to establish this variation in relation to color index of new-born infants and for the early days and months of their lives. Periods conforming to the age periods of the hemoglobin curve were selected for comparison.

Burker's Zeiss hemocytometer,¹ an approved apparatus for the more accurate counting of erythrocytes than is possible by the Thoma-Zeiss apparatus, was used in all the counts. The principles involved are somewhat different from those in force with the latter apparatus. Hayem's solution is used as the diluting fluid. Toisson's solution is not satisfactory for use with the Burker counting chamber as its viscosity is too great. The corpuscles settle rapidly in Hayem's fluid as the specific gravity of the fluid is 1.015, whereas that of the erythrocytes is 1.090. The Thoma-Zeiss capillary pipets were used. The blood was thoroughly mixed with the diluting fluid within the mixing chamber by tapping the pipet against the finger for five minutes.

In the older counting chamber the floor of the chamber is circular and the counting is done in the center of this space. The corpuscles are, therefore, counted in the center of a capillary circular film, where, on account of surface tension, their number is slightly greater than elsewhere. This source of error is avoided in the new counting cham-

¹ Burker. Pfluger's Arch f d ges Physiol **107** 426, 1905

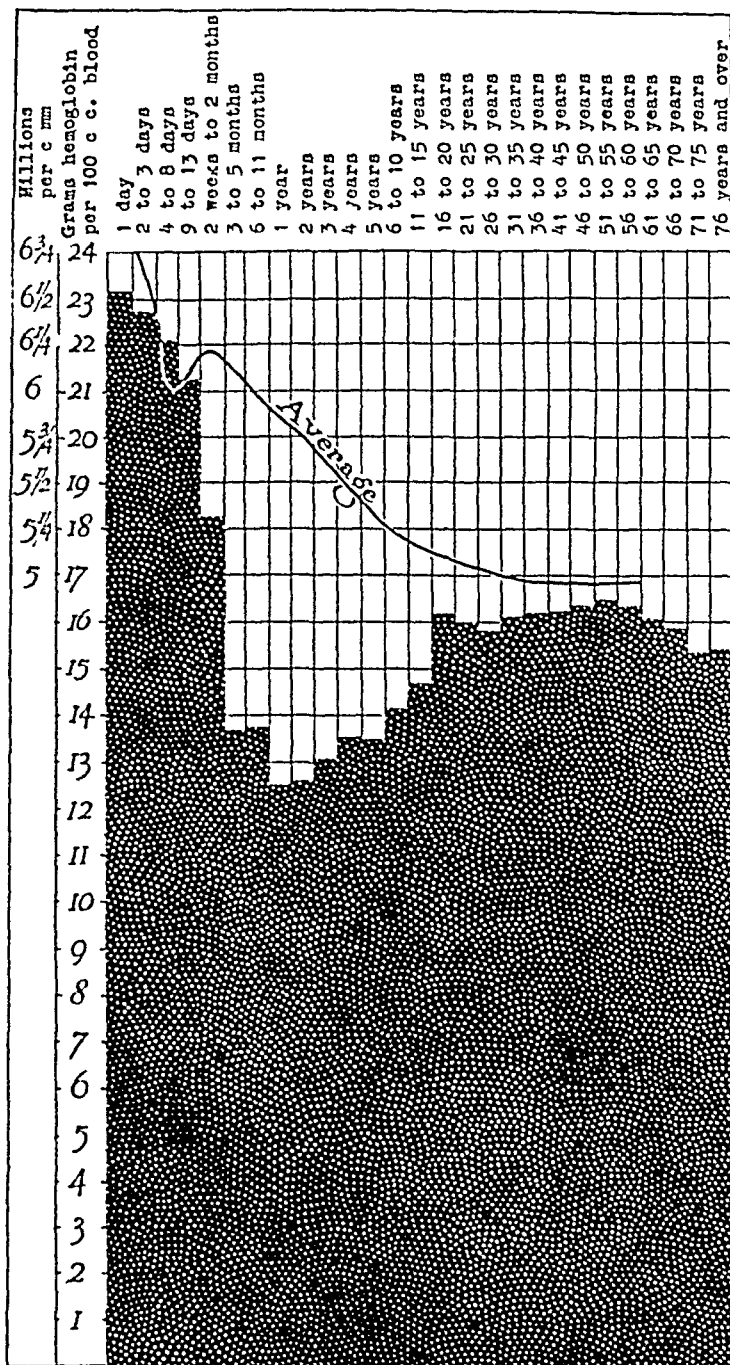


Fig 1—The solid black line indicates grams of hemoglobin per 100 c.c. of blood in persons ranging in age from one day to over 76 years. The curved line shows the average erythrocyte count at different ages to show the relationship between the number of erythrocytes and their hemoglobin content.

ber, in which the floor is represented by the upper surface of a glass 25 mm long and 5 mm wide, which is rounded off at both ends and divided into two portions by a groove 1.5 mm wide through the center. At each side of the floor piece, separated from it by a groove, is a glass plate 7.5 mm x 21 mm, of such height that the space between the floor of the cell and the cover glass placed across the plates is 0.100 mm. A cover glass 23 mm long and 21 mm wide, with rounded, polished edges, is used, so that the rounded edges of the floor project beyond it. The chamber is provided with clamps to press the cover glass firmly on both plates. The same pipets, counting chamber and cover glass were used in all this series of counts.

To determine the accuracy of my blood enumeration, I counted my own blood for five counts over a period of seven hours. Eighty squares were counted. The result of the counts and a computation of the average error by method of Gauss was as follows:

Let d equal the variation from the average

Let Sd^2 equal the sum of the squares of the individual variations

Let Fm equal the average error of the average value

Let N equal the number of observations

No of Count	d	d^2
1 530	+1	1
2 528	-1	1
3 531	+2	4
4 529	0	0
5 530	+1	1
<hr/> 529 Average		<hr/> 7 Sd^2

$$F M = \pm \frac{Sd^2}{n-1} \pm \frac{7}{4} = 1225 = \pm 11$$

As a further check to determine the variation of the blood from day to day, my blood was counted for seven consecutive mornings

No of Count	Sq of Difference from Average
1 504 + 7	49
2 471 - 26	676
3 510 + 13	169
4 503 + 6	36
5 529 + 32	1024
6 460 - 37	1369
7 501 + 4	16
<hr/> Av 497	<hr/> 6 3339
	556

$$\sqrt{556} = \pm 23.6$$

The average error = \pm the $\sqrt{\frac{SD^2}{N-1}}$ in which SD^2 is the sum of the square of the differences of the individual counts from the average count and N = the number of counts. Number of counts is seven.

$$\text{Average error} = \pm \sqrt{\frac{SD^2}{N-1}} = \frac{3339}{6} = \pm 23.6$$

Blood was obtained from the right great toe in each instance. The toe was washed with alcohol and thoroughly dried. A sharp cataract knife was used to get a free flowing drop, without pressure. The first drop was wiped away and blood for the counting secured from the second drop. The children chosen were all apparently well nourished and healthy. The cases were taken from the maternity wards of Cook County and St. Luke's Hospitals and from private cases.

It is generally conceded that there is a polycythemia at birth and that there is an increase in the first twenty-four hours. There is much diversity of opinion as to the actual number found in a cubic millimeter of blood. The average number of red blood corpuscles per cubic millimeter based on the investigations of physiologists and pathologists, is 5,742,000 red blood corpuscles per cubic millimeter of blood. The majority of the workers' conclusions for infants were based on comparatively few cases. Hayem² and Sorensen cite one case each. Buchot and Dubuisay³ show 4,300,000 as an average in six cases, Otto,⁴ four cases averaging 6,165,000, Schwinger,⁵ 5,080,765 and Schiff,⁶ 5,825,000 in single counts. Fehrsen⁷ observed forty cases—minimum 6,047,000, maximum 7,250,000. The majority of these observers used the dilution method and counted with a Thoma-Zeiss apparatus. Fehrsen's forty subjects were examined on the first and tenth days of life. Only four subjects were examined within the first two hours and nineteen were examined between the tenth and twentieth hours, with an average of 5,898,000. Womo and Dransky⁸ observed twenty-nine cases. Seven of these were not at full term and five were pathological. Six counts were made on babies before they began to breathe. His conclusions are in general similar to those of Hayem, Lepin and Schiff, namely, the number of red cells per cm. in the newborn is considerably higher than in adults and figures exceeding 7,000,000 were often obtained. He was unable to confirm the statement of Hayem and Lepin about the strict dependence between the changes in the number of red cells and the weight of the infant. This bears out my own conclusions, as I observed no relation between the number of red cells and the weight of the infant.

² Hayem, Georges. *Du Sang et de ses alterations anatomiques*, Paris, 1889, pp. 30 et seq., 189.

³ Buchot and Dubuisay. *Gaz. m  d. de Par.* 168, 1878.

⁴ Otto, R. *Pfluger's Arch. f. d. ges. Physiol.* 36 12, 27, 1885.

⁵ Schwinger, W. *Untersuchungen   ber den H  moglobingehalt u. d. Zahl der rothen und weissen Blutk  rperchen*, *Pfluger's Arch. f. d. ges. Physiol.* 72: 299, 338, 1898.

⁶ Schiff, E. *Ztschr. f. Heilk.* 11 17, 1890, *ibid.* 10, 1890.

⁷ Fehrsen, O. M. *Hemoglobin and Corpuscular Content of the Blood of the Newborn*, *J. Physiol.* 30 322, 1903.

⁸ Womo and Dransky. *Beitr  ge zur Morphologie des Blutes der Neugeborenen*. Dissertation, St. Petersburg, 1891.

In my own series of forty-one cases, I found an average of 7,630,000. Thirty-seven were taken at the time of delivery and four within two hours of delivery. Ten cases were counted on the second, eighth and fourteenth days, with an average of 6,260,000.

10 cases	14th day	Averaged	5 790			
10 "	One year	"	5 850	(Boys and Girls)		
10 "	Two years	"	5 750	" " "		
10 "	Five to ten years	"	5 210	" " "		

The highest count was 9,610,000 and the lowest was 5,060,000. The findings are expressed graphically in Figure 1, which shows, in solid black, the number of grams of hemoglobin per hundred c c in persons ranging in age from 1 to 76 years, and in the curved line, the average erythrocyte count at the same ages. In Figure 2, lines 1, 2 and 3 represent the average, maximum and minimum red blood corpuscle count in a series of forty-one cases. Lines A, B and C show the average, maximum and minimum of hemoglobin, represented by the number of grams of hemoglobin per hundred c c of blood.

The hemoglobin richness of the individual red corpuscles is known as its color index. The amount of coloring matter, i e, hemoglobin, expressed in grams per hundred cubic centimeters, in normal blood, is considered to represent 100 per cent. The average normal red cell count, i e, 5,000,000 for males and 4,500,000 for females, is considered 100 per cent. The color index is determined by dividing the percentage of hemoglobin by the percentage of red cells. In normal blood the color index is 1.

It is at once evident that four factors enter into each estimation of color index. Two of them are constants and two of them are variables, which must be accurately determined in each case. The constants are (a) The normal average number of red cells per cubic millimeter of blood, (b) the normal average number of grams of hemoglobin per hundred cubic centimeters of blood. The variables are (c) The actual number of red blood corpuscles per cubic millimeter of blood, (d) the actual number of grams of hemoglobin per hundred cubic centimeters of blood in any case under consideration.

If the results of different observers are to be compared, the same standards for constants must be employed. The averages that are recognized in the computation of color index in adults cannot be employed in determining the color index of children. It is immediately manifest, when one consults the hemoglobin values as established by Williamsor's table,⁹ that the determination of color index in children is only possible when the proper number of grams of hemoglobin for the age of the child is employed as 100 per cent. Similarly, the average

⁹ Williamsor Arch Int Med 18 505 (Oct) 1916

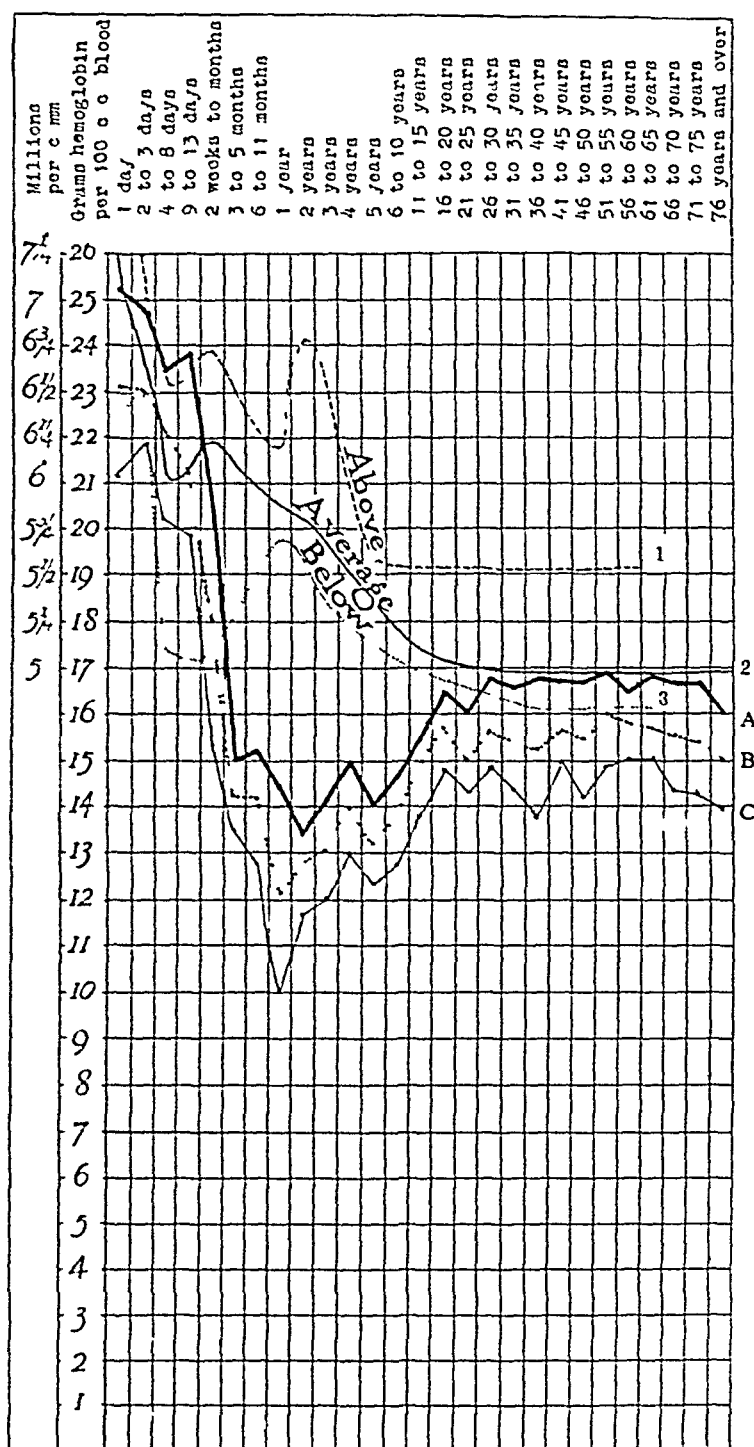


Fig 2—Lines A, B and C indicate the average amount of hemoglobin, and the average amount for those having more than the average and also for those having less than the average, for males ranging in age from 1 day to over 76 years. Lines 1, 2 and 3 show the average number of erythrocytes and the average number for those having more than the average and for those having less than the average.

number of red cells obtaining for that age must likewise be employed as representing 100 per cent. In adult males the ordinary procedure of using 5,000,000 reds and 16 gm hemoglobin is so nearly constant that these figures may be considered normal and will not give appreciable variations. The actual normal fluctuations in early life make the use of any average impossible.

CONCLUSIONS

1 The red blood count in a series of forty-one infants, in thirty-seven of whom it was taken at time of delivery, averaged 7,630,000.

2 The blood count in children 1 and 2 years of age is somewhat higher than in the adult, this being in marked contrast to the great drop in hemoglobin which is shown in Williamson's table.

3 Inasmuch as the curves of corpuscles and the hemoglobin do not run parallel to each other, the question is raised as to whether the low hemoglobin values are to be regarded as strictly normal or whether it might be altered by a different plan of infant feeding.

4 The norm employed in determining the color index of adults does not apply in determining the color index of children under 10 years of age.

INTRAVITAM BONE MARROW STUDIES PRELIMINARY REPORT

PART I

DESCRIPTION OF A MARROW TREPHINE AND EXPERIMENTAL STUDIES [†]

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During the latter part of 1920 one of us (L M M) devised a small drill carrying an outer detachable casing, the purpose of which was to trephine long bones in order to secure specimens of living bone marrow for histologic study. The problems which were opened to approach by this new method of study were undertaken jointly in 1921.

To G Ghedini¹ is conceded the credit of marrow puncture for diagnosis and prognosis. In 1910 he elaborated on this method of diagnosis in certain diseases of the blood and presented to the profession a most comprehensive article based on his experience and that of others regarding the importance of his procedure. He concludes some facts of primary importance, namely, that disease of the hematopoietic system can occur without changes in the blood and that there are many variations between bone marrow findings and those of the blood. That furthermore, severe pathology could be present for some time in the hematopoietic system without changes in the blood picture, either pre-existing, accompanying, or following, and that the frequency of such an occurrence makes old statistics unreliable because of missed cases. He advocates marrow puncture as a useful procedure.

Since this method was advocated, we have found references in some of the continental publications to bone marrow trephine as a method of diagnosis in certain atypical blood diseases, but the English and American literature is decidedly lacking in the realization of the importance of this procedure. We feel that our experience with marrow puncture, although small, might aid in placing this method before the profession.

The pathologic conditions involving bone marrow and the diseases in which bone marrow punctures might supply information of value were considered carefully. Should the method prove practical, it might be used in (1) the various types of acute and chronic leukemias, (2) atypical leukemias, chloroma and pseudoleukemia, (3) pernicious

* From the Pathological Department and Medical Clinic University of California Medical School

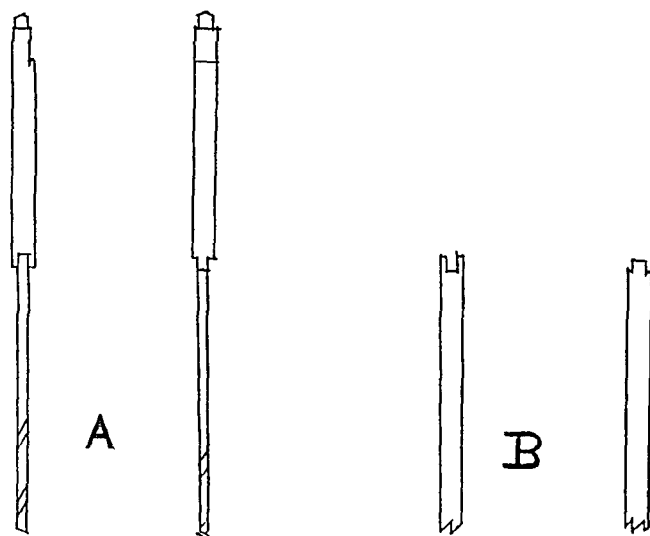
¹ Ghedini. *Wien klin Wchnsch* **23** 1840, 1910

anemia, (4) aplastic anemia, unclassified anemias, anemias due to sepsis, toxic agents, and invasion of marrow by tumor formation, chronic hemolytic jaundice and osteosclerotic anemia, (5) polycythemia and (6) purpura and allied conditions

With this field in mind, obviously the first step was to try out the feasibility of this procedure by animal experimentation. For this, an instrument smaller but identical to the one described herein and driven by a reciprocating hand drill was used.

DESCRIPTION OF MARROW TREPINE

The small trephine instrument as reproduced in the accompanying illustration is drawn to scale and represents the type used on human beings for tibia puncture. The drill proper, an ordinary steel drill (detempered), is embedded in a solid steel base, the diameter of which is identical with the standard base of an ordinary dental drill. The casing B bored from a solid steel tube of the same



Bone marrow trephine A—Drill B—Casing

diameter is of slightly shorter length than the naked drill proper and fits it snugly. The proximal circumference is longitudinally cut and fits identically into opposite grooves cut in the distal circumference of the base, into which the drill proper is set. The distal circumference of the casing is toothed and sharpened and cuts simultaneously, the drill proper preceding the casing about one-eighth of an inch. The bone dust is forced up the grooved drill inside the casing.

Technic—Both the drill proper and the casing pierce the cortex of the bone and enter the marrow cavity. The drill is then removed, leaving the casing in the marrow cavity and protecting the same from blood or other cellular tissue. In this way it is possible to obtain an uncontaminated marrow specimen. A lumbar puncture needle with approximately a third of the diameter longitudinally grooved has been used to ream the marrow confined within the lower portion of the casing as it rests in the marrow cavity. The drill is driven by a dental engine, the puncture being readily accomplished by high speed and slight pressure. A skin incision about 1 cm in length precedes the application of the drill to the bone (tibia). The entire operation is performed under local anesthesia. Silk is used to close the skin wound.

We endeavored to prove two points First, that living rabbits subjected to bone marrow puncture will show no untoward effects from such an operation Second, that marrow specimens scooped through the casing limiting the trephine opening will by histologic study reveal the true physiologic or pathologic condition of the marrow (This attempt is obviously limited to the cytology only)

From a series of six healthy rabbits, the blood pictures of which totaled within normal limits for red and white blood cells and differential counts,² femur punctures were made under aseptic conditions and the marrow smears studied histologically

Technic for Marrow Smears and Cultures—The marrow specimen removed from the casing is small in amount and dries quickly when exposed to the air To insure against cellular distortion we smear the marrow specimen immediately after its withdrawal upon sterile coverslips, float face downward in methyl alcohol for fixation and stain by May-Grunwald-Giemsa and Wright's methods For section comparison Wolbach's modification of the Giemsa method or a combination of May-Grunwald and Giesma stains was used after the fixed marrow (two parts saturated mercuric chlorid solution and one part absolute alcohol) had been run down to water and immersed in methyl alcohol

For cultural work we attempted aspiration of the marrow by a Luer syringe with a nonbeveled needle Difficulty was always encountered in aspiration, usually the specimen contained much blood and little marrow Such specimens may be used for marrow cultures in bacteriologic work but are decidedly unfit for histologic study Thus far we have used the more common culture mediums in our attempts to grow organisms from such preparations

The puncture wounds healed without infection in about two weeks The animals were then killed by ether inhalation Superficial examination at the site of the small trephine opening showed healing of advancing degrees In no case was the pathologic picture at the trephine site of any marked importance as noted by the unaided eye In a single case the wound (superficial) was infected, but the bone and marrow cavity was uninvolved

In all cases the marrow was fixed and studied in section and compared with the smears obtained during life The smears resembled the marrow sections as to cell type and content Allowance, however, was made in smear preparations for mature red blood cells present, which are constant and vary according to the number of ruptured sinuses produced by trauma in obtaining the marrow

2 There is much normal variation in rabbit's blood

Bunting's³ experiments on rabbits poisoned with saponin were repeated, in part, with successful blood pictures of blastic crises. Such a series of experiments gave opportunity to study erythrogenic activity in both megaloblastic and normoblastic phases. Both marrow smears and subsequent sections showed a profound action of the poison on the erythroblastic tissues. The activity of the red cell elements was more marked the longer the animal was kept under the influence of nonlethal doses of the marrow toxin. In all cases an experimental anemia was produced, giving pictures of blastic crises whenever saponin was injected intravenously.

Following these experiments, we undertook others designed for more careful study of red blood cell activity. Selling's⁴ work on rabbits with benzol was reproduced, in part. When a leukopenia of from two to three thousand per c mm is produced, then injections of saponin bring forth blastic activity in the blood interpreted as a profound toxic action on the marrow. The regenerative activity approaches a purer type of small and large premature red blood cell elements, the leukoblastic cells being held largely in abeyance by the toxic action of benzol. It was felt that by so doing a histopathologic marrow picture simulating primary anemia might be approached more closely.

In our study of the white blood cell elements we produced continued leukocytosis over varying periods of time by making subcutaneous abscesses (turpentine) or infection of the peritoneum. In one rabbit small injections of staphylococcus were given intravenously daily. In some animals we were successful in producing a fairly marked (from 14,000 to 15,000) leukocytosis for a week or more.

Our interpretation of the marrow smears and sections led us to believe that the leukopoietic elements were in predominance, certainly in marked contrast to the experiments with saponin. The marrow smears and sections checked well. None of the animals showed untoward results, although one rabbit was subjected to puncture four times at two-day intervals for study of the developmental myelocytoses. One animal sustained a spontaneous fracture of the femur in this series.⁵

Such preliminary work gave opportunity to study both white and red blood cell activity in the bone marrow by study of smears obtained

³ Bunting J. Exper. M. **6** 624, 1906.

⁴ Selling. Beitr. z. path. Anat. u. z. allg. Path. **51** 576, 1911.

⁵ We attempted no work on fowl leukemia. It was felt that such a condition might well be diagnosed from a marrow puncture, realizing in the pathology of the disease a marked myeloid hyperplasia in the bone marrow.⁶

⁶ Ellermann. Verhandl. d. Deutsch. Path. Gesellsch. **12** 224, 1908. Ellermann & Bang. Ztschr. f. Hyg. u. Infektionskr. **63** 231, 1909. Schmeisser. J. Exper. M. **22** 820, 1915.

from the same and to check such preparations against microtome sections of the same marrow in the same phase of white or red celled hyperplasia

These preliminary experimental studies lead directly to the field of marrow pathology in the human, more particularly cellular activity in the long bones

CONCLUSIONS

1 An instrument has been devised for perforating the cortex of the long bones in animals and human beings to obtain specimens of living marrow for histological study

2 We have demonstrated on animals that the method is feasible and safe

3 We feel that the specimens of marrow obtained by this method are satisfactory for microscopic study, but occasional dilution with blood makes the specimen difficult to interpret. The smears from the marrow checked up with postmortem preparations fixed and sectioned

INTRAVITAM BONE MARROW STUDIES

PART II

SURVEY OF THE CLINICAL FIELD ^{*}

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In Part I we demonstrated that bone marrow puncture in animals is a comparatively simple and harmless procedure and that it is a feasible and practical method of studying (in rabbits) both normal and pathologic bone marrows, yielding nearly as much information as fixation and sectioning of marrow obtained postmortem. Before proceeding to the clinical application of this method, on the patient, it became necessary to satisfy ourselves regarding certain questions that were uppermost in our minds during the experimental work.

1 *Can the puncture be accomplished without pain and discomfort to the patient and is it safe?*—After trying it out several times on cadavers, we became convinced that the cortex of the tibia could be pierced easily and quickly. We felt that it would be a simple matter to anesthetize the skin and periosteum so that the procedure would be practically painless. The question of safety will be dealt with later but, of course, the final answer can only be given after the method has been tried in a large series of cases.

2 *Can enough accurate data be obtained by this method to offset a certain amount of unavoidable discomfort to the patient and what will the patient benefit by this method of study?*—In order to answer the first part of this question, it was necessary to peruse the literature on the anemias and the leukemias to ascertain whether previous investigators had felt a need for this procedure in the course of their studies and, above all, to find reported cases in which we felt that this method would have supplied the data necessary to make a diagnosis during life. Several of these reported cases are included in this communication. We believe that in certain types of cases it is necessary to know what is taking place in the marrow in order to arrive at a correct diagnosis. Regarding the possible benefit to the patient, it must be acknowledged that in the majority of cases it will not affect the final issue. Yet it must be conceded that it is only by accurate study and recognition of bone marrow pathology during life that we can hope to arrive at means for influencing such pathology.

^{*} From the Pathological Department and Medical Clinic, University of California Medical School.

examination has failed to reveal changes in the bone marrow is correct in the majority of cases, although the accumulation of carefully studied material since that date is large

Walz, Pappenheim and Bradenburg through their investigations arrived at similar conclusions, namely, that the bone marrow in every case of leukemia is the primary seat of the disease and the origin of the cells which give the characteristic microscopic appearance to the blood and that the other organs are only secondarily involved in the general hyperplasia of the lymphadenoid tissue which occurs³

According to Neumann all cases of leukemia can be differentiated by the evidence in the bone marrow Naegeli, Ziegler, Sternberg⁴ and others take exception to this Naegeli, contrary to the belief of Pappenheim, is not of the opinion that the origin of all lymph cells is from the bone marrow, especially in those cases showing large lymphatic tumors peripherally and only islands of lymphatic tissue in the bone marrow

Cases of leukosarcoma⁴ fall under this category While the marrow in many cases is infiltrated with lymphatic (?) cells giving a negative oxydase reaction, nevertheless, the intense hyperplasia as noted in the bone marrow in leukemia is not described Herxheimer⁵ believes that leukosarcoma is only a stage of lymphatic leukemia, Paltauf believes the evidence against, while Sternberg adheres to the origin of the tumor masses as being neoplastic in nature and considers the blood picture as an invasion of tumor cells distinct from lymphocytes Webster,⁶ in a review of twenty-six cases, arrives at the conclusion that the disease is not neoplastic in nature but a direct response on the part of the lymphocytes to a chemotactic influence exerted by the disease causing agent, and the infiltration of lymphocytes in the bone marrow is comparable to similar cell accumulations elsewhere in the body

On the other hand, there are cases of lymphatic leukemia which run their course without clinical or pathological evidence of involvement of lymph glands or other lymphoid tissue Such a case is reported by Reed⁷ and later discussed by Ehrlich The lymphoid tissue throughout the body was unaffected but the bone marrow was practically entirely composed of lymphocytes Ehrlich expressed his opinion that such a leukemia might originate from any substratum of lymphoid tissue, such as that in the skin, in the intestinal wall, or in the bone marrow⁷

Similarly Domarus has described a certain type which has been designated medullary lymphadenoid aleukemia in which the bone

³ Reed *Am J M Sc* **124** 653, 1902

⁴ Sternberg *Beitr z Path Anat u z allg Path* **61** 77, 1916

⁵ Herxheimer *Muench med Wchnschr* **60** 2506, 1913

⁶ Webster *Johns Hopkins Hosp Bull* **31** 458, 1920

⁷ MacCullum *A Textbook of Pathology*, Ed 2 W B Saunders, Philadelphia, p 835

Variations of such marked degree may lead to differences of opinion regarding diagnosis. Furthermore, the qualitative blood findings may occasionally fail. This is of decided prognostic importance in dealing with cases of leukopenic leukemia and aplastic anemia. One such case will be reported later. In such variable cases a bone marrow puncture offers opportunity for making a diagnosis. A conclusion based on the pathology of the disease is our most accurate means of diagnosis at the present time, and the cellular content of the long bone marrow is the most constant single pathologic index of either type of leukemia and in any phase of this disease.

Atypical Cases of Leukemia—In a few cases reviewed from the literature a marrow puncture would have been of decided advantage in arriving at a correct conclusion premortem. Our experience with such cases is small, only two having come under our observation for bone marrow puncture.

Ewald¹³ reports the case of a male, aged 37, with six weeks of illness, intense anemia, large spleen, no glandular enlargement. Blood findings: hemoglobin 28 per cent, red blood cells 740,000, white blood cells 800, differential count: neutrophils, 71 per cent, large lymphocytes, 2 per cent, small lymphocytes, 21 per cent, myelocytes, 3 per cent, transitionals, 3 per cent. Necropsy: Typical picture of leukemia with characteristic changes in the marrow and organs. Marrow smears contained large numbers of typical myelocytes, occasional lymphocyte and occasional nucleated red cell.

Beltz¹⁴ (Case 4) Female, aged 30. Remained in hospital five months until death. On admission: red blood cells, 2,270,000, white cells, 2,500. A later count showed red cells, 1,440,000, white cells, 2,500, the differential count: neutrophils, 10 per cent, large lymphocytes, 11 per cent, small lymphocytes, 36 per cent, large mononuclear cells, 10 per cent, myelocytes, none, premature large mononuclears, 34 per cent. Terminally: white cells 101,800, with 78 per cent premature large mononuclear cells. Necropsy: Long bone marrow brownish red. Microscopically, the most numerous cells were myeloblasts. Findings typical of myeloid leukemia.

Sternberg¹⁵ (Case 1) Female, aged 20. Ten days after vaccination complained of fever, stomatitis and hemorrhages. Examination showed a large spleen and normal liver. Blood count: red cells, 1,950,000, white cells, 3,400, differential count: neutrophils, 12 per cent, lymphocytes, 87 per cent, many normoblasts. Blood culture: short chained streptococcus. Necropsy: femur marrow firm and reddish color, smear showed occasional streptococcus, many large lymphocytes and a few small nongranular cells with negative oxydase reaction. A few retroperitoneal lymph glands were enlarged and others on the right side of the neck. Diagnosis: Lymphatic leukemia.

Beltz¹⁴ (Case 9) (Reference is made to this case to show the fallacy of absolute reliance on a bone marrow puncture.) Female, aged 43, died five days after admission to the hospital. Admission blood count: red cells, 1,440,000, white cells, 12,150, 72 per cent of which were lymphocytes. Two days later: red cells, 1,370,000, white cells, 7,600. Terminally, the whites rose to 27,400. Necropsy: Patches of red cellular marrow in the fatty marrow of the long bones. histologic picture that of myeloid leukemia but definite lymphoid follicles.

13 Ewald. Berl klin Wchnschr **43** 870, 1906.

14 Beltz. Deutsch Arch f klin Med **113** 116, 1913.

15 Sternberg. Wien klin Wchnschr **26** 553 (June) 1920.

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15 Sternberg. Wien klin Wchnschr **26** 553 (June) 1920

noted in addition. It is easily conceivable that a marrow puncture in this case may have led to incorrect conclusions, depending on whether myeloid, lymphoid or fatty marrow was removed.

The converse of this case, lymphatic aleukemia with stimulation and blood stream invasion of myelocytes, makes a differential diagnosis impossible (Hirschfeld⁸). A marrow puncture in such an instance might lead one astray if such a specimen was isolated from myeloblastic islands.

One might argue in the same manner regarding cases of so-called leukanemia. Following Pappenheim, the lymphatic or myelogenous



Fig 1—Smear of bone marrow from a case of myeloid leukemia. Patient, aged 12 years. Specimen diluted with physiologic solution of sodium chloride. Shows eosinophilic myelocytes and mitotic cells of the white cell series. This patient presented a leukemic blood picture.

overgrowth in the bone marrow is always primary and the megaloblastic and normoblastic activity are explained by the leukopoietic infiltration and crowding out of the red cell elements the remainder of which undergo a compensatory hyperplasia.

One of the first of such cases was described by Leube and Arneth (quoted from Morawitz¹⁶).

Male, severe anemia, died during third week. Blood normoblasts and megaloblasts and a slight increase in the leukocytes, 13 per cent of which were myelocytes and a few polymorphonuclear cells without granulation. Necropsy. Myeloid metaplasia of the marrow. Liver showed no evidences of siderosis.

These few more or less exceptional cases are referred to for completeness. Such cases only exceptionally alter the textbook picture of

leukemic long bone marrow which is no longer fatty but firm, opaque, yellow gray, pinkish gray or reddish and homogeneous (Figs 1 and 6) The hyperplasia is constant in the long bones in both the lymphoid and myeloid type, but we noted less hyperplasia in some cases in the marrow of the tibia as compared with the femur In the acute leukemias there is practically always a very marked increase of cells in the long bone marrow but not as constant as in the chronic forms In a few cases only part of the long bone marrow may show infiltration (Naegeli¹⁰) These cases are classed as exceptional

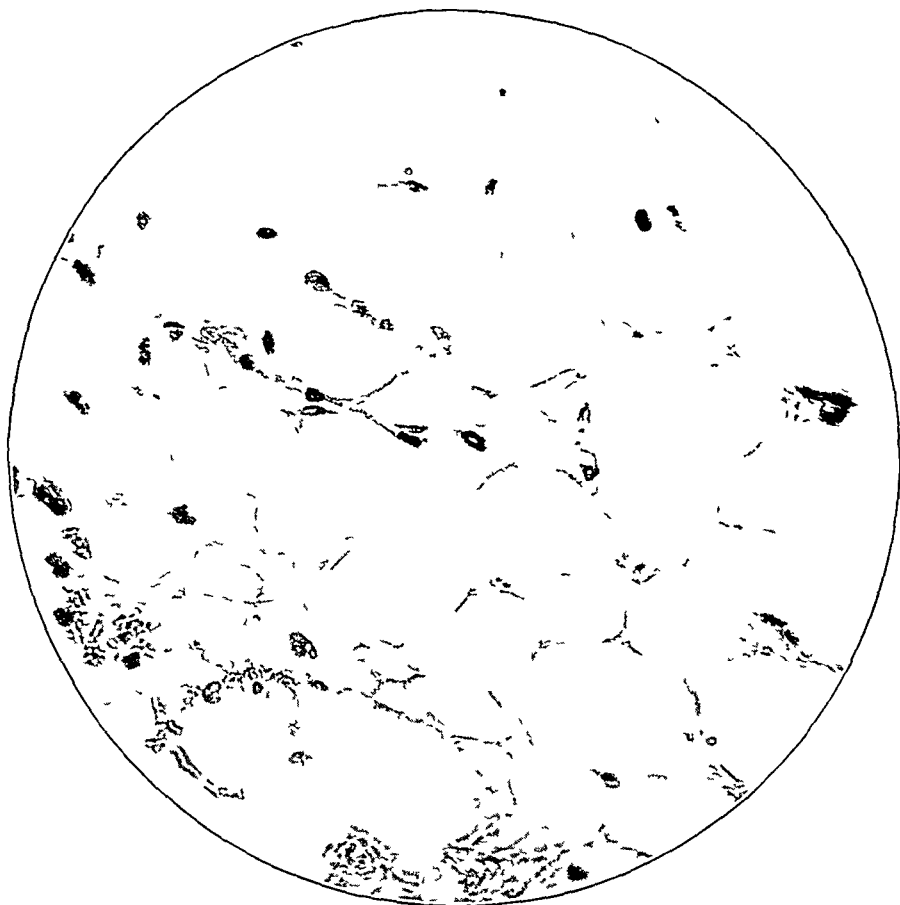


Fig 2—Normal adult long bone marrow from the tibia Subject aged 18 years

APLASTIC ANEMIAS

The experimental work of Blumenthal and Morawitz (quoted by Kleinschmidt¹⁷) in regard to aplastic anemias is of interest They found that in dogs and rabbits repeated blood lettings brought about a disappearance of the erythroblastic and myeloid tissues with abundant increase of the lymphoid elements, that is, changes in the bone marrow which have close connection with those of aplastic anemia in man The

¹⁷ Kleinschmidt *Jahrb f Kinderh* **81** 1, 1915

increase of the lymphoid elements is of paramount importance and their relative increase in a leukopenic blood brings the question of a leukopenic leukemia into the differential diagnosis. On clinical grounds one cannot distinguish all such cases from leukemia. We quote three cases, one of Hirschfeld,¹⁸ one of Engel and Lipowsky and a third of Jagie and Schiffner. It is felt that with such pathology a bone marrow puncture would have been of marked importance in ruling out leukopenic leukemia.

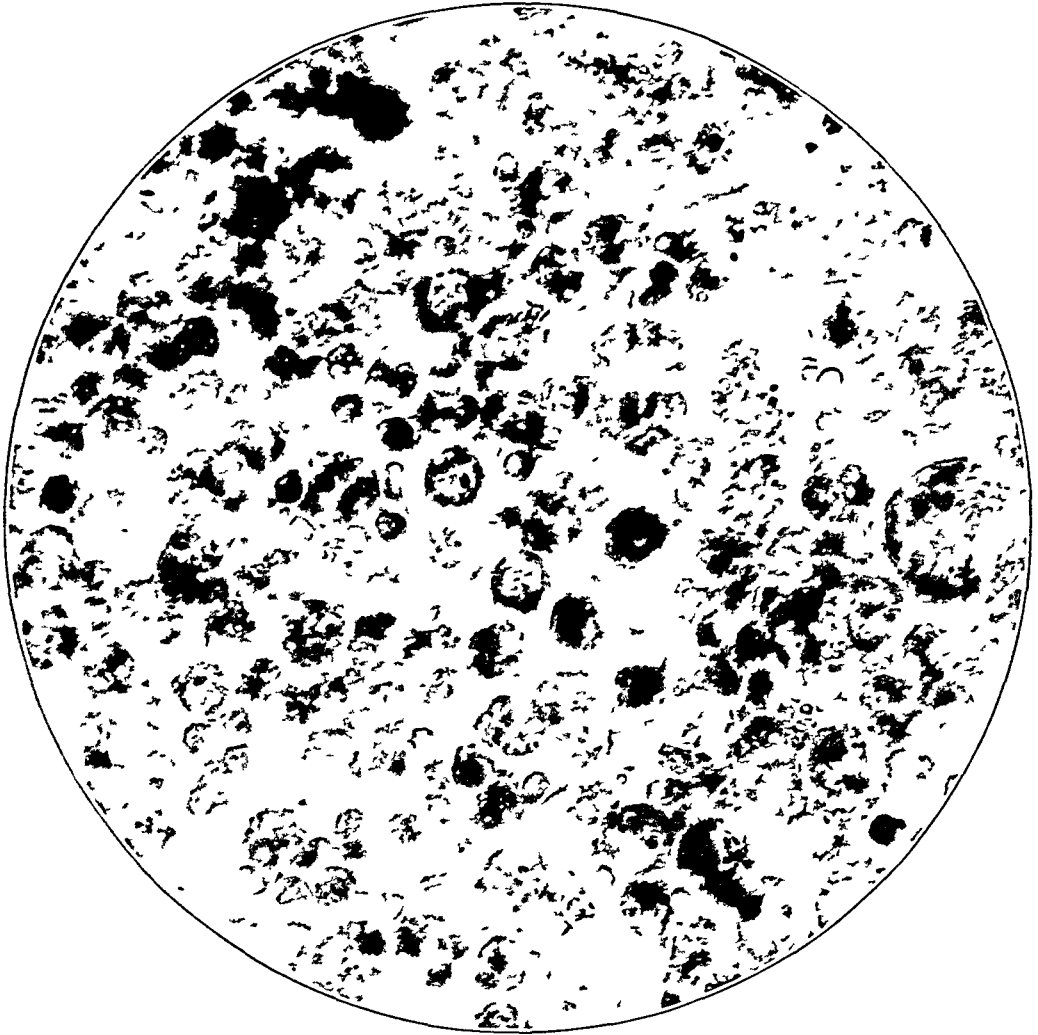


Fig 3—Myeloid leukemia. Section taken from bone marrow of femur.

Female, aged 28. Shortly after labor developed progressive anemia with a hemorrhagic diathesis. Disease progressed for four months. Twelve days before death blood count showed red cells, 1,200,000, white cells, 3,600, 72 per cent of which were lymphocytes, no normoblasts or megaloblasts. Necropsy. Severe anemia, femur marrow fatty throughout. Ribs—red liquid material showing almost pure lymphocytes, rarely a nucleated red.

Patient entered hospital with hemorrhagic diathesis. Blood count red blood cells, 2,000,000, hemoglobin, 18 per cent, no nucleated reds and leukopenia, 90

18 Hirschfeld. Berl klin Wchnschr 43 545, 1906

per cent of white cells were lymphocytes. Death occurred on the eighth day after admission. Necropsy. Yellow fatty marrow in the long bones. Ribs showed many bacteria and were of dirty grayish color.¹⁸

Female, aged 18. Her illness dated three weeks previously. On entering hospital, bleeding, pallor and enlarged spleen. Blood count: red cells, 2,000,000, white cells, 10,000, 90 per cent of which were lymphocytes. Shortly before death: red cells, 650,000, white cells, 2,400, hemoglobin, 12 per cent, differential count 74 per cent lymphocytes. Necropsy. No evidences noted of lymphomatosis.¹⁵

A somewhat similar case of anemia of the aplastic type was one seen by Dr. L. Porter at the Children's Hospital in San Francisco. Through his kindness we punctured the marrow of the tibia and were able to arrive at a correct diagnosis. A synopsis of the case is as follows:

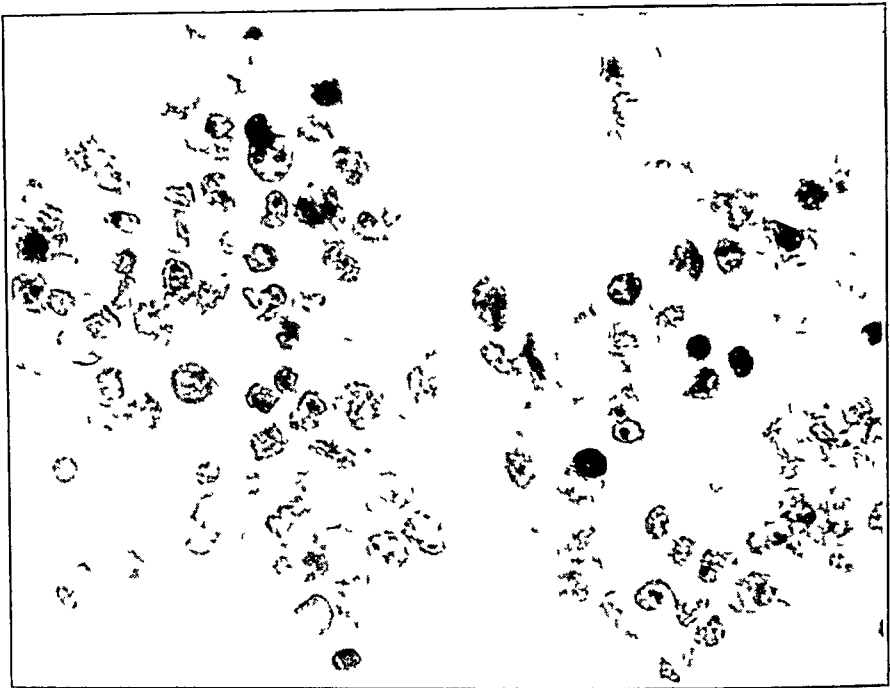


Fig. 4—Section of bone marrow from femur from a case of sepsis with purpura

CASE 1—R. J., male, aged 4 years

Family History—No hemophilia, mother's sister insane

Past History—Full term, 6½ pounds birth weight, normal delivery. Influenza two years ago

Present Illness—Child was well until a month ago when he developed fever during the night. Was confined to bed for two days and tired and drowsy afterward. Seventeen days ago again had fever during the night, subsequently progressively got paler. Three days ago had a large hemorrhage from the nose which could not be stopped without packing.

Physical Examination—Well grown, markedly pale. Mucous membranes, nares bloody, swollen lips, cervical adenopathy, tonsils small, no stomatitis. Heart and lungs negative, save for a few rales at the bases. Spleen two fingers breadth below left costal margin, liver not enlarged. Skin. No ecchymoses noted. Blood count: Hemoglobin, 32 per cent, red cells, 1,790,000, white cells, 850, differential count 1 per cent neutrophils, 97 per cent lymphocytes, 2 per cent large mononuclear cells, marked anisocytosis, poikilocytosis, achromia,

platelets reduced, no nucleated reds, many microcytes. The admission temperature was 40 C. Remained elevated for five days and dropped by lysis. All other tests were negative. Marrow puncture on the third day showed an absolutely fatty marrow devoid of marrow cells. No myeloid cells were seen in any of the smears. A few lymphocytes, identical to the type as found in the blood and giving a negative oxydase reaction, were noted in conjunction with normal red blood cells. No blasts or giant cells seen. (For comparison see Figure 6, leukopenic leukemia.)

This marrow picture readily ruled out leukemia and was so decidedly aplastic as compared to the long bone marrow in a normal child that a tentative diagnosis of aplastic anemia was made. Cultures from the bone marrow remained sterile. Transfusion of citrated blood and iron was the only means of therapy. The hemorrhages were arrested, the change in blood count was remarkable.

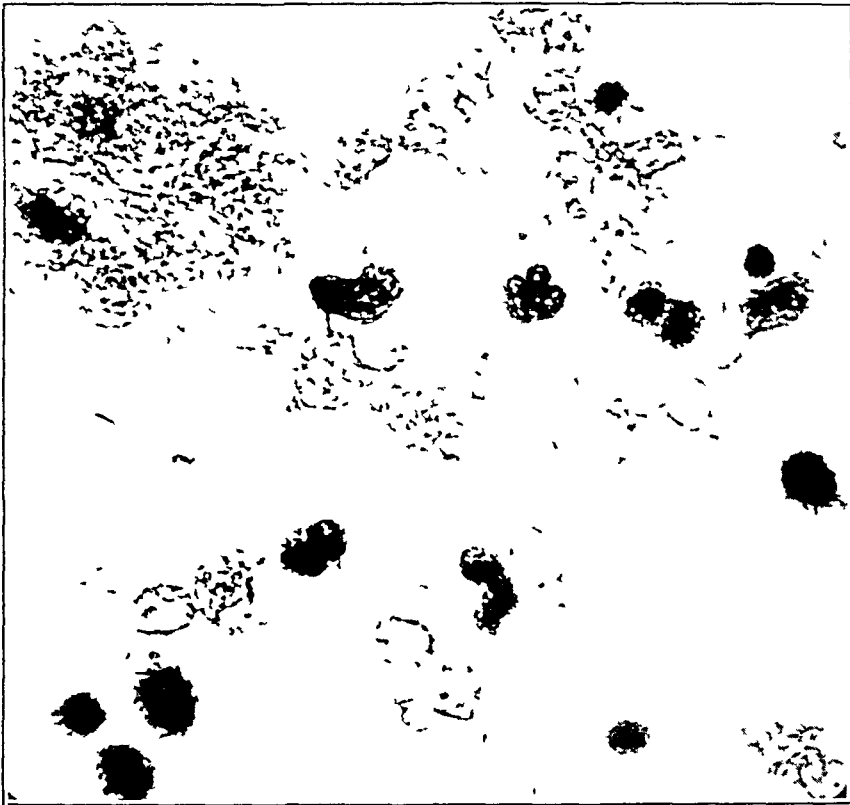


Fig 5—Bone marrow from tibia of a case of pernicious anemia. The outlined red blood cells are a constant and unavoidable part of such a postvital preparation. Note the dividing cells of the red cell series.

and the child left the hospital three weeks after admission with much regained strength and a blood count as follows: Hemoglobin, 65 per cent; white cells, 5,300; neutrophils, 55 per cent; lymphocytes, 35 per cent; and 10 per cent reticulated red cells. A later count, a month after discharge, showed hemoglobin, 62 per cent; red cells, 3,790,000; white cells, 11,500; color index, 0.81; polymorphnuclear neutrophils, 60 per cent; eosinophils, 1 per cent; large lymphocytes, none; small lymphocytes, 28 per cent; large mononuclears, 6 per cent; myelocytes, 5 per cent. Both macrocytes and microcytes present with moderate poikilocytosis. Reticulated reds, about 3 per cent. The child continued to improve temporarily, relapsed and died in the second month of its illness. No postmortem was done.

ETIOLOGY OF THE LEUKEMIAS

Before concluding this brief résumé on the subject of leukemias, the etiology of the disease might well be considered. Briefly stated, tumor formation (Banti) or an abnormal response of the myeloid or lymphoid tissue to recent or latent infections are points much discussed. Advocates of an infectious etiology include such men as Hertz, Pappenheim, Pawlowsky, A. Fraenkel, Ziegler, Jockman, Wilbur and Sternberg.

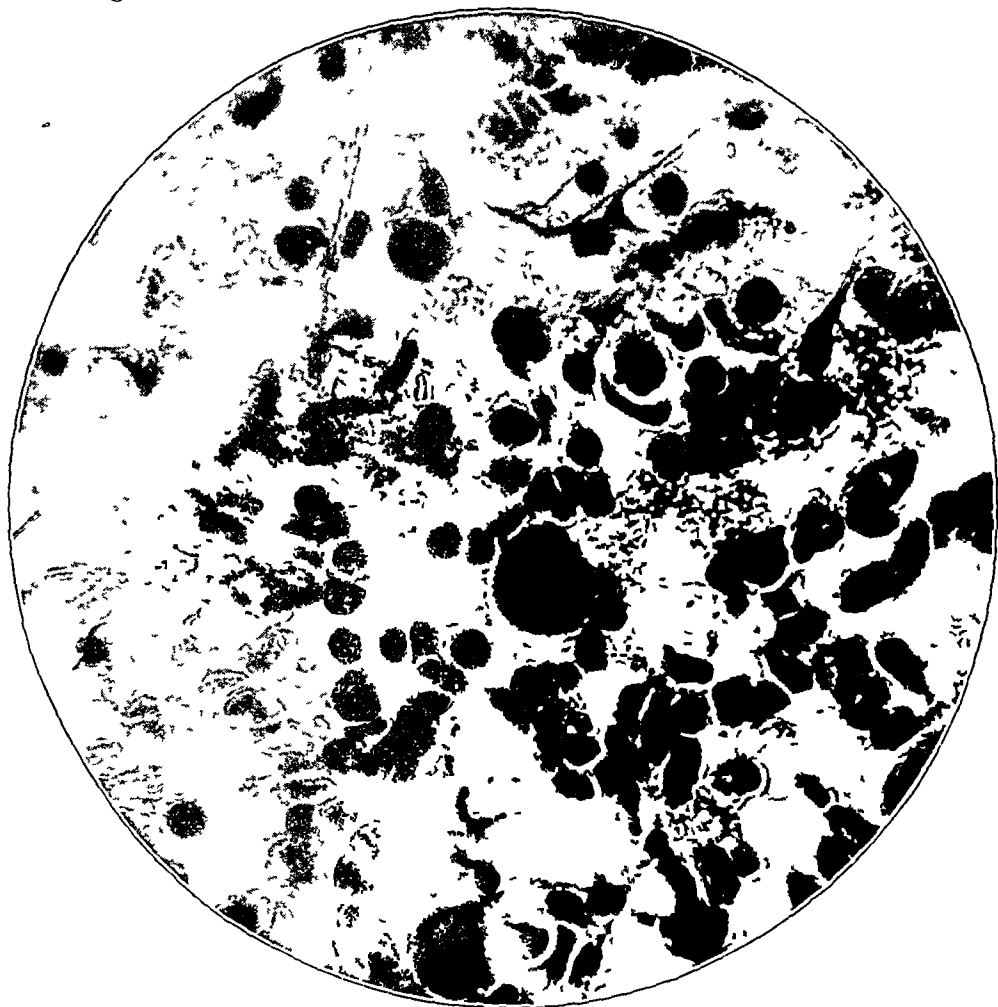


Fig 6—Bone marrow smear taken from tibia in a case of myeloid leukemia. Myeloblasts, myelocytes, nucleated red cells and undifferentiated cells (stem cells) are seen. This patient presented a leukopenic blood picture and the diagnosis was made from the marrow smear. The patient was 9 years of age.

That the clinical picture of acute leukemia with temperature elevation, stomatitis, purpura, hemorrhage, anemia and glandular and splenic enlargement constitutes a group which parallels certain of the severe septic states is not doubted. Furthermore, the termination of many of the chronic forms of leukemia may present a similar picture. To such an extent is this true that very recently Sternberg¹⁵ stated as his belief

that acute leukemias do not exist as an entity but are all on a chronic basis. It is thus important, following Naegeli, to know whether or not the blood count was normal previous to an acute leukemia.

Various types of organisms have been described as occurring in the blood or tissues, the seat of leukemic changes. In a far greater proportion of cases no etiology is forthcoming. Sternberg,¹⁹ after isolating a diplostreptococcus from some of his cases, was unable to produce leukemic pathology in rabbits. (He likewise failed with staphylococcus and pneumococcus.) Pappenheim, Naegeli and Hirschfeld emphasize the fact that the blood pictures in some cases of general bacterial infection are identical with those of acute myeloid leukemia, the only difference being the issue. These changes probably represent a biologic reaction of the hemopoietic system to various nonspecific, generally septic infections which, as a rule, call forth a leukocytosis, under certain circumstances, however, a myelocytosis.

Cases reported by Cabot,²⁰ Jackson and Smith,²¹ Turk and Ludke (quoted by Sternberg¹⁹) are quoted as infectious states presenting leukemic blood pictures with recovery. Even mechanical irritation of the bone marrow (multiple fractures of leg—Simon²²) has given rise to a leukemic blood picture. Other cases of infectious disease with many premature white cells in the blood, but death occurring from the disease per se are noted (Stevens²³). We have recently seen a child of 12 with a well advanced empyema of the left chest cavity (streptococcus) and 48 per cent myelocytes in the blood smear.

After severe infections which normally call forth a high leukocytosis (pneumonia for example) it is not uncommon after the crises to find from 4 to 5 per cent myelocytes in the blood. In children this is more common and in infants under 1 year, according to Rotch and Morse,²⁴ the presence of myelocytes in sick children is without significance. Histologically one finds at this age the long bone marrow richer in cellular content than the sparsely cellular fatty long bone marrow of the adult, the marrow of the ribs in older individuals giving origin to practically all the red and white cells (Fig. 2).

Wherein lies the difference in the fatal prognosis of the leukemias and the questionable outcome of septic states with leukemic blood pictures? Is it because in leukemia the marrow proliferation is due to a disturbance of the mechanism governing cell production rather than a response to chemotaxis in the ordinary sense? In this connection it is

19 Sternberg. *Wien klin Wchnschr* **24** 1623, 1911.

20 Cabot. *Osler and McCrae Modern Medicine*, **4** 676.

21 Jackson and Smith. *Boston M. & S. J.* **172** 136, 1915.

22 Simon. *Am. J. M. Sc.* **132** 144, 1906.

23 Stevens. *Lancet* **2** 791, 1902.

24 Rotch and Morse. *Boston M. & S. J.* **152** 729, 1905.

not an uncommon clinical observation to observe in patients with myeloid leukemia suffering with intercurrent infections, an aleukemic or subleukemic blood picture and diminution in the size of the spleen. We recently observed a patient with myeloid leukemia suffering from pneumonia with a blood count comparable in all respects with the leukocytosis of the disease and with a relative diminution in the size of the spleen to the extent that during observation of the pneumococcus infection leukemia was not suspected by the attending physician. During the postconvalescent stage, however, the blood picture again became leukemic and the spleen increased markedly in size.

The pathologic differentiation between bone marrow hyperplasia in continued septic states and that of myeloid leukemia is at times difficult. The most outstanding feature is the degree of hyperplasia of the marrow (Figs 3 and 4).

"Only by further bacteriologic and perhaps protozoologic studies of the blood, bone marrow, spleen and lymph glands of such patients and by animal inoculation from the tissues involved including bone marrow trephined from the living bone can we clarify the problem." Following Wilbur's²⁵ quoted suggestion regarding the etiology of acute leukemia, marrow cultures were taken from two persons trephined during life and the material subjected to the ordinary cultural methods. Each failed to show any bacteriologic growth. This evidence is decidedly inconclusive, the work is to continue when opportunity presents.

We are well aware of the work of Ward²⁶ and his arguments and conclusions against the infectious origin of the leukemias. At present we offer nothing in refutation.

In conclusion, we must leave the field of leukemias as reviewed. We have drawn from the literature certain atypical cases, the diagnoses of which might have been made more certain by marrow puncture. Such a series must of necessity be grouped from reports, as individual experience in a single clinic does not cover such a field.

PRIMARY ANEMIA, SECONDARY ANEMIA, POLYCYTHEMIA

The question of the value of "intravital" bone marrow studies in pernicious anemia was approached with a conservative state of mind, as we felt that such studies would throw no light on the etiology of the disease. We assume bone marrow changes, in pernicious anemia, as being secondary to the causal factor or factors, but we believe it is important in both diagnosis and prognosis to determine what is taking place in the bone marrow. Such study will improve our diagnostic criteria and serve to separate, at an earlier period, those anemias with

25 Wilbur J A M A 65 1255 (Oct 9) 1915

26 Ward Brit J Child Dis 14 10, 1917

a clinical picture of pernicious anemia but due to sepsis, syphilis, malaria, recurrent hemorrhages, carcinoma of the stomach, carcinoma and sarcoma involving bone marrow, anemias due to intestinal parasites, etc., etc

That the need of such studies is felt may be inferred from the statement by Minot²⁷ "The pathology of the bone marrow has not been studied as one might wish. Future studies may decide whether or not there is any absolutely distinctive feature of it that is associated only with pernicious anemia."

The phase of this disease in which bone marrow studies will probably be of most value is prognosis. Our prognostic criteria at present are dependent largely on blood studies, it being assumed that at any given period the pathologic elements in the peripheral circulation are an index of what is occurring in the bone marrow. Experimental work in animals, in part, bears this out, notably the work of Bunting,²⁸ who, by injecting ricin into rabbits, was able to reproduce the marrow picture of pernicious anemia. The following quotation elucidates this point:

Applying these conclusions to pernicious anemia, it seems possible that an analagous (to ricin) toxin may be present destroying red cells both in the circulation and in the marrow so that in the reaction nucleated red cells are used to supply the deficiency—that further action of the toxin reduces the erythropoietic groups more or less to the megaloblastic centers, diminishing greatly the regenerating power of the marrow and resulting in a discharge of megaloblastic cells in the hasty effort to supply the needs of the circulation. Thus the regular orderly development of the groups of the marrow cells is interfered with and a short cut is taken from the megaloblast to the macrocyte, an imperfect immature cell, as shown by its polychromatophilia and granular basophilia. In this light it is not difficult to see why cases of pernicious anemia with few normoblasts and more megaloblasts in the circulation are of graver prognosis than those with a large number of normoblasts and few megaloblasts, and, again, if one regards the presence of nucleated cells in the circulation as evidence of injury to the bone marrow, one has an explanation for the "nucleated red cells crises" of pernicious anemia and leukemia in which the blood picture resembles much that is shown in ricin intoxication.

These observations and deductions seem to Bunting to offer "a not unsatisfactory explanation of the so-called reversion of the marrow to the embryonic type in pernicious anemia."

It has been well established that at times, and in certain stages of the disease, critical blood studies give fairly satisfactory information as to what is occurring in the bone marrow. Our marrow punctures in pernicious anemia, up to date, have not yielded much information in addition to that gained from a careful study of the history of the case and careful blood studies. This was due, in great part, to the type of case selected. We have performed marrow puncture in five cases of

27 Minot. *Oxford Medicine* 2, 1920

28 Bunting. *Johns Hopkins Hosp. Bull.* 36 222, 1905

pernicious anemia In one case three punctures were made, in another case two punctures were made, making eight punctures in all Three of these cases showed a red marrow with few cells and no signs of division These three cases were of long standing and had been in a state of relapse for several months Two patients survived the last puncture only about six weeks, one lived for about three months after examination of the marrow One case presented a pinkish grey marrow, with a moderate amount of cellular activity and very few megaloblasts Subsequent study and observation of the case cast some doubt on the accuracy of the diagnosis of pernicious anemia These three cases with inactive marrows would seem to belong to the class of case termed by Minot and Lee²⁹ the myelotoxic type This type of case is undoubtedly the least promising for bone marrow study

In the earlier types of cases if the ratio between blood destruction and cell regeneration can be estimated a fairly definite prognosis can be made Various methods have been devised to estimate hemolysis or blood destruction Bone marrow studies will give a fairly accurate conception of the phase of regeneration One of our patients, a male, aged 40, a laborer, belonged to the earlier type of case He had had two very satisfactory remissions in two and one-half years since the onset of his illness During these remissions he was able to earn his livelihood by manual labor During the two weeks in hospital before we saw him he had an intermittent temperature, from one to two degrees above normal He had urobilin in the urine and showed signs of hemolysis His red cells numbered less than two million with a high color index and the blood smears showed a moderate number of regenerative forms The marrow smears showed a red marrow with abundant signs of cellular activity In Figure 5 some of these cells are shown We felt that this man would have a satisfactory remission He left the hospital in about three weeks very much improved We believe that in this case the marrow gave somewhat more accurate information than blood studies had furnished

In certain atypical cases, marrow studies will probably be of considerable practical importance For example, Ellermann³⁰ has been impressed in his studies on the histology of pernicious anemia by the presence in certain cases of considerable numbers of myelocytes in the marrow and in the liver and spleen He mentions myelocytes as being plentiful in the marrow in every instance in his series of twelve cases studied postmortem Minot²⁷ mentions the fact that there are cases in which a great outpouring of immature white cells and blasts occurs, the white count in some cases reaching as high as 50,000, causing an incorrect diagnosis of leukemia to be made

²⁹ Minot and Lee Boston M & S J **177** 761, 1917

³⁰ Ellermann Acta Med Scandinavica **53** 718, 1919

The whole picture is much more sharply defined in these cases if one knows what is occurring in the bone marrow

There are other hemolytic and septic anemias in which bone marrow studies may yield information of practical value. We have studied the marrow postmortem in a case of sepsis with severe hemorrhage (Fig 4). The protocol at necropsy stated that clinically the patient had an aplastic bone marrow, as no regeneration forms were found in the blood. Bone marrow from the femur, sectioned and studied microscopically, shows a remarkable picture of activity. One or more transfusions in this case might have turned the balance in favor of the patient.

It has occurred to us in connection with bone marrow studies in pernicious anemia and other anemias that certain vital staining methods, such as employed by Evans³¹ in vital staining of endothelial leukocytes might yield information of value in determining the origin of the different types of cells found in the marrow. Such studies are in progress, as well as staining work to determine the presence or absence of deposits of hemosiderin in the marrow in pernicious anemia.

At this point it may be well to call attention to the fact that we do not advocate bone marrow puncture in pernicious and other anemias as a method to supplant blood studies, but merely as an additional source of information in selected cases.

Another field of some promise for the application of marrow puncture is that of the polycythemias. It is usually possible clinically to separate polycythemia vera with splenomegaly from symptomatic polycythemia. It will be possible to collect data in the former type of case bearing on the question of whether, as suggested by some,³² the bone marrow is the site of the disease. This is a question of some importance as other investigators, notably Blumenthal,³³ report cases in which a necropsy was performed and a fatty bone marrow was found showing no alterations. We have investigated one case of over two years' duration with red cell counts reaching as high as 12,000,000. This patient had a left-sided hemiplegia resulting from a cerebral hemorrhage and also a rather large hemorrhage into the orbit on one side. There was no demonstrable enlargement of the spleen. Marrow puncture in this case showed a fatty marrow with no evidence of cellular activity. The whole question of bone marrow findings in polycythemia is in need of further study and perhaps revision.

DISCUSSION

It has been our purpose in this preliminary note to present the method, establish its feasibility and outline its scope of usefulness.

31 Evans. *Anat Rec* 8 98, 99, 1914

32 Weber & Watson. *Internat Clin* 4 47, 1905

33 Blumenthal. *Bull de l'Acad Roy de med de Belgique*, Ser 19, 1905-4

There are certain phases of bone marrow study, certain possibilities that we have had in mind but have not touched on in this paper. We have no data and the considerations are, therefore, purely theoretical. We refer to bone marrow cultures in septic anemias and in generalized sepsis in which organisms are not always present in the peripheral circulation. Chronic and subacute endocarditis may be taken as a type example. Certain cases of chronic malaria in which no plasmodia can be demonstrated in the peripheral circulation may yield plasmodia in bone marrow smears. We have such a case under investigation now. Clinically, the patient presents an enlarged spleen with a leukopenia and an anemia. There is a past history of syphilis and of malaria. The possibilities for the employment of the method are many but it may be argued that it is too dangerous and too much of a surgical procedure to be practical. We believe that with ordinary care and asepsis in technic the danger of infection is very slight. With the use of local anesthesia to the skin and periosteum the patients do not complain of pain and discomfort. It is hoped that in centers where material is available for study, the method will be employed and data collected to determine whether or not it deserves a place among recognized procedures for clinical investigation.

THE BASAL METABOLISM IN NONTOXIC GOITER AND IN BORDERLINE THYROID CASES

WITH PARTICULAR REFERENCE TO ITS BEARING IN
DIFFERENTIAL DIAGNOSIS ¹

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An extended study of the basal metabolism in its relation to the clinical features of toxic goiter ¹ has been in progress in this clinic since June, 1914. As a by-product of this work there has been collected a considerable amount of data on patients with clinically nontoxic goiter and on patients without frank hyperthyroidism or hypothyroidism, but in whom the possibility of one of these conditions was suspected, and also on patients with a variety of pathologic states not including the thyroid. Since the use of the basal metabolism determination as a test of thyroid function has come into rather wide use in the last two or three years, it has seemed to us advisable to place these data on record. A large amount of data on normal persons, which, as regards the thyroid problem, serves as normal control data, has been secured by Benedict of his associates ². Our own data presented here are in the nature of pathologic controls.

Between June 10, 1914, and Oct. 22, 1921, one thousand patients were observed in the metabolism laboratory at the Massachusetts General Hospital, and on these, 2049 determinations were made. The methods used have been discussed in previous papers. The Benedict apparatus has been used from the beginning—until July, 1921, the universal type,³ since then the portable ⁴. Up to May, 1917, we determined both carbon dioxide and oxygen, and made the calculation of heat produc-

* From the Medical and Surgical Services of the Massachusetts General Hospital, aided, in part, by a gift from Dr. William Norton Bullard.

1 Means, J. H. Basal Metabolism and Body Surface, *J. Biol. Chem.* **21** 263, 1915. Studies of the Basal Metabolism in Disease and Their Importance in Clinical Medicine, Boston M. & S. J. **174** 864, 1916. Hyperthyroidism Toxigenic Goiter, *M. Clin. N. America* **3** 1077, 1920. Determination of the Basal Metabolism as a Method of Diagnosis and a Guide to Treatment, *J. A. M. A.* **77** 347 (July 30) 1921. Means, J. H., and Aub, J. C. Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, *J. A. M. A.* **69** 33 (July 7) 1917. Basal Metabolism in Exophthalmic Goiter, *Arch. Int. Med.* **24** 645 (Nov.) 1919.

2 Harris, J. A., and Benedict, F. G. A Biometric Study of Basal Metabolism in Man, Carnegie Inst. Washington, Pub. 279, 1919.

3 Benedict, F. G. Ein Universalrespirationsapparat, *Deutsch. Arch. f. klin. Med.* **107** 160, 1912.

4 Benedict, F. G., and Collins, W. E. A Clinical Apparatus for Measuring Basal Metabolism, Boston M. & S. J. **183** 449, 1920.

tion from the respiratory quotient obtained. Since then we have determined oxygen only and used an assumed respiratory quotient of 0.82. The Sage Institute standards have been used in determining variations from the normal.⁵ For the purpose used we believe the above procedure is sufficiently exact. For certain problems in metabolism it might not be. The Benedict apparatus, despite various criticisms in the literature, has proved highly satisfactory in our hands. Boothby and Sandiford⁶ have suggested that it is not sanitary. We have never seen evidence to substantiate this, and we should like to point out that with the latest type of apparatus there is no chance for infection.⁴ The possible sources of infection are the mouthpiece itself, water of condensation in the tubing, and the air contained in the apparatus. The mouthpiece, of course, is always sterilized by everyone. Water of condensation that might run back from piping to patient, in the portable Benedict is found solely in the F shaped metal member to which the mouthpiece is attached. We have adopted the custom of always boiling this metal member with the mouthpiece, and recommend this practice to others. The air is entirely refreshed between patients by raising and lowering the spirometer bell several times.

In our series of one thousand cases there are included most of those cases of disturbed thyroid function that have come to the hospital during the period covered, for it has become a routine to follow the basal metabolism of patients being treated for hyperthyroidism or hypothyroidism. We also have a group of borderline thyroid cases in which the metabolism was determined as an aid in differential diagnosis, a series of patients with blood diseases, various endocrine diseases other than those of thyroid origin, and a group of miscellaneous nonendocrine conditions. These 1,000 cases were distributed as follows: Clinically thyrotoxic, 300 cases; clinically myxedema and cretinism, 32 cases; goiters clinically nontoxic, 102 cases; borderline cases in which hyperthyroidism was suspected, 290 cases; borderline cases in which hypothyroidism was suspected, 70 cases; other endocrine diseases, 41 cases; blood diseases (anemia, leukemia and polycythemia), 66 cases; miscellaneous nonendocrine diseases, 99 cases.

It is our purpose at the present time to discuss these cases only in so far as they bear on the question of the value of the determination of the basal metabolism in the diagnosis of thyroid activity. Certain of the groups will be discussed in detail in later papers.

Subnormal Metabolism—We first studied the occurrence of subnormal metabolism. This is generally considered one of the cardinal

⁵ Aub, J. C., and DuBois, E. F. Clinical Calorimetry, Nineteenth Paper. The Basal Metabolism of Old Men, Arch. Int. Med. **19**: 823 (June) 1917.

⁶ Boothby, W. M., and Sandiford, I. Basal Metabolic Rate Determinations, Philadelphia, W. B. Saunders Co., 1920.

laboratory signs of myxedema and cretinism Of the thirty-two cases of these diseases there were twenty-six which had received no thyroid All of these twenty-six cases showed a reduction below minus 10 per cent in the metabolic rate The average findings in the several types included in this group are shown in Table 1

TABLE 1—BASAL METABOLISM IN MYXEDEMA AND CRETINISM

Type	Number of Cases	Average Basal Metabolic Rate, Per Cent
Spontaneous myxedema	16	—25
Roentgen ray myxedema	4	—21
Cachexia strumipriva	2	—17
Cretinism	4	—19

This finding, namely, that a low metabolism occurs in 100 per cent of the untreated cases which show the clinical picture of myxedema or cretinism, would seem to prove that a low metabolism is an essential feature of those diseases

We next looked into the occurrence of subnormal metabolism in conditions other than frank myxedema and cretinism After excluding these conditions, there were found to be sixty-three cases with basal metabolic rates of —11 per cent or lower The degree of reduction, and the relative number occurring in each group, are shown in Table 2

TABLE 2—OCCURRENCE OF SUBNORMAL METABOLISM

Basal Metabolic Rate, Per Cent (Inclusive)	Group Number of Cases							Per Cent
	Suspected Hyperthyroidism	Non-toxic Goiter	Miscellaneous Non-Endocrine	Suspected Hypothyroidism	Other Endocrines	Blood Diseases	Total All Groups	
—11 to —12	5	3	5	8	3	1	25	40
—13 to —14	3	2	2	3	3	0	13	20.5
—15 to —16	2	1	1	2	7	0	13	20.5
—17 to —18	1	0	0	0	3	0	4	6.5
—19 to —20	0	0	0	0	1	0	1	1.5
—21 or less	1	0	0	2	3	1	7	11
Total with subnormal rates	12	6	8	15	20	2	63	100.0
Total cases in group	290	102	99	70	41	66	668	
Per cent of group with subnormal rates	4.1	5.9	8.1	21.4	48.8	3.0	9.3	

This table shows that subnormal metabolism in diseases other than those of the endocrine glands is distinctly infrequent Of the sixty-three cases studied, fifty-three, or 84 per cent, were either definitely endocrine or presented some clinical suggestion of endocrine disease Furthermore, of the ten nonendocrine cases, eight showed rates between —11 and —14 per cent, hence their degree of subnormality was

slight Also, grouping endocrine and nonendocrine cases together, 81 per cent of all the cases have rates between — 11 and — 16 per cent, which is higher than any of the myxedema averages

The group of endocrine diseases other than thyroid includes suprarenal and pituitary abnormalities, and it is known that in hypopituitarism there sometimes is a reduction in the basal metabolism⁷ There seems also to be one in Addison's disease⁸ The group of blood cases shows that in anemia, polycythemia and leukemia, subnormal metabolism is a distinct rarity

Supernormal Metabolism—In a similar way we studied the occurrence of supernormal metabolism Of the 300 cases showing definite clinical signs and symptoms of hyperthyroidism (except in certain instances after operation or roentgen-ray treatment) there was but one case (0.3 per cent) which failed to show a metabolic rate of more than +10 per cent, and that patient had very mild symptoms

The occurrence of supernormal metabolism in the remaining cases is shown in Table 3

TABLE 3—OCCURRENCE OF SUPERNORMAL METABOLISM

Basal Metabolic Rate, Per Cent (inclusive)	Group Number of Cases							Per Cent
	Non- toxic Goiter	Sus- pected Hypo- thyroid- ism	Miscel- laneous Non Endo- crine	Other Endo- crines	Sus- pected Hyper- thyroid ism	Blood Dis- eases	Total All Groups	
+61 to +90	0	0	0	0	0	2	2	1
+41 to +60	0	0	0	0	6	10	16	8
+26 to +40	0	1	2	1	17	9	30	15
+19 to +25	0	3	5	3	22	10	43	21
+15 to +18	1	2	5	1	27	8	44	22
+11 to +14	12	3	8	5	33	6	67	33
Total with supernor- mal rates	13	9	20	10	105	45	202	100
Total cases in group	102	70	99	41	290	66	668	
Per cent of group with supernormal rates	12.7	12.9	20.2	24.4	36.2	68.1	30.2	

Aside from clinical hyperthyroidism, the greatest incidence of supernormal metabolism is in the group of blood diseases This is consistent with the findings of several observers that there is practically always an increase in leukemia⁹ and not infrequently in the severe

⁷ Boothby, W. M. The Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77** 252 (July 23), 1921

⁸ Aub, J. C. An unpublished research

⁹ The literature on this point is summarized by Murphy, J. B., Means, J. H., and Aub, J. C. Clinical Calorimetry, Twenty-third Paper. The Effect of the Roentgen Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, Arch. Int. Med. **19** 890 (June) 1917. See also Gunderson, A. H. The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, Boston M. & S. J. **185** 785, 1921

anemias¹⁰ The group showing the next greatest incidence is that of cases not presenting the full clinical picture of hyperthyroidism, but some suggestion of that condition This is not surprising Of the other endocrine 24.4 per cent show slight elevations

The twenty cases (20.2 per cent) out of ninety-nine in the miscellaneous nonendocrine group need some comment There were two cases each with a rate of $+26$ per cent (none higher) One of these patients was a woman seven months pregnant When seen four months later during lactation the rate was $+13$ per cent The other patient with a rate of $+26$ per cent did not keep absolutely quiet during the test One patient with a rate of $+23$ per cent had malignant lymphoma of the neck Two weeks later after vigorous roentgen-ray treatment her rate was $+14$ per cent Another patient with a $+23$ per cent rate had paralysis agitans It was thought that the tremor might well explain this elevation, as a week later when he was quieter it was -2 per cent Rates of $+21$ per cent were found in a case of osteitis deformans and in one of questionable chlorosis A second test on this patient three months after the first test showed a rate of $+14$ per cent In one case of paroxysmal tachycardia during the paroxysm there was a rate of $+20$ per cent The remaining thirteen cases had rates not higher than $+18$ per cent Their supernormality, therefore, was slight

Nontoxic Goiter—Coming now to the group of 102 clinically nontoxic goiter cases, the average basal metabolism rate was with regard to sign, $+2$ per cent, and without regard to sign, ± 6.4 per cent As we have pointed out elsewhere,¹¹ in making averages of this sort the average with regard to sign indicates whether there is a positive or negative bias in the series (in this instance a very slight positive one), and the average without regard to sign, the general degree of normality of the series, as shown by the prevailing magnitude of the variations This series of nontoxic goiters from the metabolism point of view shows a very high grade of normality It compares in that respect very favorably with a group of thirty-one normal men studied by Carpenter et al.² This latter group showed average rates as follows with regard to sign, -1.7 per cent, without regard to sign, ± 5.1 per cent

A result such as this in nontoxic goiter makes one wonder whether the thirteen of these 102 cases that showed rates greater than $+10$ per

10 Meyer, A. L., and DuBois, E. F. The Basal Metabolism in Pernicious Anemia. *Clinical Calorimetry*, No. 15, *Arch. Int. Med.* **17**: 965 (June), 1916.
Tompkins, E. H., Brittingham, H. H., and Drinker, C. K. The Basal Metabolism in Anemia, with Especial Reference to the Effect of Blood Transfusion on the Metabolism in Pernicious Anemia, *Arch. Int. Med.* **23**: 441 (April) 1919.

11 Means, J. H., and Woodwell, M. N. Remarks on Standards for Normal Basal Metabolism, *Arch. Int. Med.* **27**: 608 (May) 1921.

cent, or the six that were lower than —10 per cent, were not really suffering from either a mild grade of hyperthyroidism in the first instance or of hypothyroidism in the second instance

We searched further, to see whether the different types of nontoxic goiter showed any constant tendencies, but without finding any such. The series was divided into several subgroups, and the average rates obtained are shown in Table 4

TABLE 4—NONTOXIC GOITER

Type	Number of Cases	Metabolism Variation With Regard to Sign, per Cent	Metabolism Variation Without Regard to Sign, per Cent
Adenomata	38	+2.7	±6.9
Cystic	11	+1.2	±5.0
Diffuse enlargements	37	+1.1	±6.3
Diffuse enlargements in adolescents	16	+2.1	±7.1

There was no conspicuous tendency for the cases showing subnormal or supernormal rates to fall exclusively into any of these subgroups

Suspected Hypothyroidism—The average figures for the group of seventy patients who clinically were suspected of having hypothyroidism, but in whom the entire picture of frank myxedema was lacking, were with regard to sign, —1.4 per cent, without regard to sign, ± 8.7 per cent

The negative bias here is slighter than the positive bias in the previous group, but there is a larger proportion of cases with abnormal metabolism. Nine, for example, show rates of +11 per cent or higher, and fifteen show rates of —11 per cent or lower. A certain number of low rates we should expect, but the high ones are, perhaps, a little surprising, but if we examine them closely we can in several instances find adequate explanations. For instance, one case with a rate of +26 per cent had some signs suggesting myxedema, but others suggesting acromegaly. A second with a rate of +24 per cent had a picture suggesting myxedema, but was taking large doses of thyroid at the time the test was made. A similar explanation can be found for one of the cases showing a rate of +15 per cent.

Suspected Hyperthyroidism—The last group, that of cases suspected for some clinical reason—nervousness, tachycardia, or other such manifestation—of having hyperthyroidism, showed, as is not surprising, a somewhat greater variation. There were 290 cases in this group, and the average rates were with regard to sign, +7.1 per cent, without regard to sign, ± 10.2 per cent.

Here there is a somewhat greater bias (positive) than we have met before, but still it is not so very large. The individual variations too tend to be larger than in the previous two groups. For example, there are 105, or 36 per cent, which show rates higher than $+10$ per cent, and twelve, or 4 per cent, with rates lower than -10 per cent. A survey of the twelve with subnormal metabolism shows that they were all cases in whom the suggestion of hyperthyroidism was very slight. They were a type in which hyperthyroidism was a possibility in the mind of the clinician rather than a probability, and the metabolism test was made for exclusion only. Coming now to the 105 with supernormal metabolism we find that forty-four of them have rates between $+11$ per cent and $+16$ per cent, sixty between $+11$ per cent and $+18$ per cent, and eighty-two between $+11$ per cent and $+25$ per cent. Seventy-eight per cent, therefore, showed elevations of a slight grade only. A further investigation shows that of the 105 cases, seventy-five, or 71 per cent, had but one metabolism test performed. An analysis of these 105 cases, case by case, is hardly worth while. A considerable proportion of them very likely really were suffering from hyperthyroidism. The rest were cases of psychoneurosis, effort syndrome, organic heart disease, in which because of nervousness or tachycardia or some such sign the clinician wished to exclude thyrotoxicosis. Of the thirty cases in which more than one test was made, there were ten in which a second test was performed within a fortnight after the first. In each case the second test was lower, the average of the first tests being $+37$ per cent, and of the second $+18$ per cent.

DISCUSSION

Our object here has been to shed light on the merit of the determination of the basal metabolism as a functional test of the thyroid. On this problem, of course, only indirect evidence can be had from human beings. Our findings, however, in nontoxic goiter and borderline thyroid cases, added to those already recorded in the literature, we believe furnish some indirect evidence of value.

In the first place, it seems clear that in untreated myxedema and cretinism there is invariably a subnormal metabolism, the average rate in our twenty-six cases being -23 per cent. After treatment with thyroid the rate rises toward normal.

In the second place, in patients showing definite clinical signs of hyperthyroidism there is invariably a supernormal metabolism, and as has been shown elsewhere, the degree of elevation runs roughly parallel to the intensity of the symptoms and signs.¹

Of course, it may justly be said that to consider metabolic rates varying more than 10 per cent above or below the standard abnormal,

and those that vary less than 10 per cent not abnormal, is an entirely arbitrary procedure. It is arbitrary but, nevertheless, reasonable. A line must be drawn somewhere for purposes of analysis. This 10 per cent limitation covers the known facts very satisfactorily, therefore, its use serves a good purpose. But in interpreting the significance of basal metabolic rates in patients it must be borne in mind that there is no absolute line of demarcation between normal and abnormal metabolism. We should have no hesitancy in saying that a rate of $+80$ per cent (provided there was no technical error), or one of -25 per cent, was pathologic, but we could not say so with certainty in regard to one of $+16$ per cent or -14 per cent.

A certain number of patients with other kinds of endocrine disease, pituitary, suprarenal, etc., show subnormal metabolism, but in persons without clinical evidence of endocrine disease, subnormal metabolism is distinctly uncommon, and when it does occur the degree of depression is slight as compared with frank myxedema and cretinism.

Supernormal metabolism in conditions other than clinical thyrotoxicosis is more frequent. It nearly invariably occurs in leukemia, and often in the severe anemias and polycythemias. Except in the group of blood diseases, the elevation is generally slight as compared with toxic goiter. It should be pointed out that fever is often accompanied by an elevation of the basal metabolism, but the present analysis is based on afebrile patients.

Our series of 102 patients with goiter, but without clinical signs or symptoms of hyperthyroidism or hypothyroidism, shows nearly as high a grade of normality as does Carpenter's series of normal men. Our average for the group was $+2.04$ per cent. It is also interesting to note that Boothby⁷ with an entirely different technic got an average of $+2$ per cent in a series of 254 similar cases.

In other words, in clinical hyperthyroidism we find increased metabolism, in clinical hypothyroidism decreased metabolism, and in goiter clinically nontoxic we find an essentially normal metabolism. One might ask, therefore, whether the determination of the metabolic rate added anything to our knowledge of such cases. Perhaps it does not, in so far as diagnosis is concerned, except to add a quantitative impression of the severity of the disease which is of distinct help in following its course and the effect of treatment. It is in the borderline group of cases, that is to say, those cases with symptoms or signs that suggest the possibility of abnormal thyroid function, that the metabolic rate determination really helps in diagnosis.

Our group of cases of suspected hypothyroidism, on the whole, shows a high grade of normality of metabolic rate, and of the patients that did have subnormal rates several showed improvement in symptoms

on being given thyroid. In the group of suspected hyperthyroidism cases there is a higher incidence of abnormal metabolism, but even here two thirds of the cases were within the normal range. Whether the remaining third showing supernormal rates were really thyrotoxic we cannot say. We feel that probably many of them were, their clinical pictures being highly suggestive.

We must point out that with many of our patients (that is to say, in those where the test was made for diagnostic purposes) a single test only was performed. There is no doubt that the first test in certain subjects, particularly those at all alarmed by the procedure, does not give a true basal value. The work of Aub and his associates¹² suggests that this may be due to an increased flow of epinephrin. In doubtful cases second, and if necessary third tests (on different days) should be made. When errors occur, however, they are always in the direction of giving too high values. Leaks in the apparatus, restlessness or alarm on the patient's part, all tend to increase the observed metabolism.

We feel, therefore, that the finding of normal rates in persons suspected of having hyperthyroidism practically rules that condition out, but the finding of an elevated rate does not necessarily rule it in. The safest procedure and one which we carry out wherever possible is, on finding an elevation in rate in a person with questionable clinical picture, to repeat the test, until a constant reading on different days is obtained. When a base line for the given patient is reached, then the interpretation may be made. In our experience, however, it is extraordinary what a large proportion of patients show normal rates on the first observation. It is the exception rather than the rule to have to make repeated tests. We should like to emphasize that to get a true basal rate in new patients their confidence must be secured, and all details of technic carefully carried out. The matter of complete rest and the postabsorptive state on the part of the patient are of the utmost importance. So too is the taking of the body temperature and the recognition of the elevations that fever may cause. No one should attempt to make metabolism determinations who is not familiar with the principles of calorimetry and the why and wherefore of each step in the procedure, and a clear understanding of the pitfalls that may occur.

The finding of subnormal rates is rather simpler. A rate probably cannot be lowered by extraneous factors. Low rates mean abnormal metabolism, they are not open to the possibility of being artefacts, as high rates are.

In general, we feel from the mass of data now in the literature as well as from our own experience that high rates mean hyperthyroidism,

12 Aub, J. C., Bright, E. W., and Forman, J. Metabolic Effect of Adrenalectomy on the Urethanized Cat, *Am J Physiol* **61** 349 (July) 1922.

provided a few well recognized other causes for increased metabolism, leukemia, anemia, acromegaly, fever, etc., are ruled out, and that low rates mean hypothyroidism provided hypopituitarism, Addison's disease, starvation, etc., are ruled out. There seldom should be any great difficulty in excluding the conditions other than thyroid which alter the metabolic rate, they are few in number and present fairly obvious clinical signs.

CONCLUSIONS

1 Patients with an outspoken clinical picture of hyperthyroidism invariably show increased metabolism, and those with definite clinical pictures of hypothyroidism invariably show decreased metabolism. Those with goiters, but no signs or symptoms of abnormal thyroid function, for the most part show normal metabolism.

2 Patients with atypical or incomplete clinical evidence of abnormal thyroid function may show normal or abnormal metabolism. The majority show normal metabolism.

3 By inference from the indirect evidence we believe that in these borderline thyroid cases, provided that in the first place a true basal rate is secured, and, provided that certain well recognized causes for increased metabolism, such as fever, acromegaly, leukemia and severe anemia are excluded, the finding of an increased basal metabolic rate is strong presumptive evidence of hyperthyroidism. In a similar way, provided that such conditions as starvation, hypopituitarism, and hypoadrenalism are excluded, a low metabolic rate is strong presumptive evidence of hypothyroidism.

4 To that extent, then, the metabolism test is distinctly useful in differential diagnosis. Like all other laboratory tests it should only be interpreted with due regard to all other clinical and laboratory findings, and with due regard for its limitations and pitfalls.

We are indebted to Miss Catherine Thacher and Miss Margaret N. Woodwell for making a considerable number of the metabolism tests.

THE ALKALIMETRY OF WHOLE BLOOD

SECOND PAPER THE ACID FIXING POWER OF THE BLOOD IN RENAL DISEASE *

JOHN B RIEGER, M D, AND HUGO A FREUND, M D

DETROIT

Our present conception of the physiologic acid-base equilibrium, resting largely on the work of L J Henderson,¹ assigns to the kidney the principal rôle in maintaining the normal alkalinity of the body fluids. So adequate is the healthy kidney in this respect that the production of acid within the body may be increased to many times the basal amount, as, for example, during great muscular exertion and in the ketosis of diabetes mellitus, without sensibly reducing the bicarbonate content of the blood.

Indeed, from the work of Straub and Schlayer,² Lewis and his co-workers,³ of Peabody,⁴ Whitney,⁵ MacNider,⁶ Gettler and St George,⁷ Chace and Myers,⁸ and others, it appears that no appreciable reduction of the blood bicarbonate occurs, until the function of the kidney, as determined by the conventional tests, has been affected gravely. Acidosis, defined as a condition of lowered blood bicarbonate, appears, then, to be of little importance in the diagnosis of renal insufficiency.

* The first paper, "The Alkalimetry of Whole Blood—A Preliminary Study," by John B Rieger, appeared in the *J Lab & Clin M* **5** 668 (July) 1920.

1 Henderson, L J. Das Gleichgewicht zwischen Basen und Säuren im tierischen Organismus, *Ergebn d Physiol* **8** 254, 1909, A Critical Study of the Process of Acid Excretion, *J Biol Chem* **9** 403, 1911, The Theory of Neutrality Regulation in the Animal Organism, *Am J Physiol* **21** 427, 1908.

2 Straub, H, and Schlayer, K. Die Uramie eine Saurevergiftung? *Munchen med Wchnschr* **59** 569 (March 12) 1912.

3 Lewis, T, Ryffel, J H, Wolf, C G L, Cotton, T, and Barcroft, J. Observations Relating to Dyspnea in Cardiac and Renal Patients, *Heart* **5** 45 (Oct) 1913.

4 Peabody, F W. Studies in Acidosis and Dyspnea in Renal and Cardiac Disease, *Arch Int Med* **14** 236 (Aug) 1914.

5 Whitney, J L. Studies on Acidosis, the Immediate Cause of Death, and Remarks on the Acidosis of Nephritis, *Arch Int Med* **20** 931 (Dec) 1917.

6 MacNider, DeB Wm. A Study of Renal Function and the Associated Disturbance in the Acid-Base Equilibrium of the Blood in Certain Experimental and Naturally Acquired Nephropathies, *Arch Int Med* **26** 1 (July) 1920.

7 Gettler, A O, and St George, A V. The Value of Modern Blood Chemistry to the Clinician, *J A M A* **71** 2033 (Dec 21) 1918.

8 Chace, A F, and Myers, V C. Acidosis in Nephritis, *J A M A* **74** 641 (March 6) 1920.

Hoesslin,⁹ Sellards,¹⁰ Palmer and Henderson,¹¹ however, from their studies of the effect of alkali administration on the reaction of the urine, concluded that a condition of acidosis exists in the incipient nephropathies as well as in a great variety of other pathologic conditions, and often occurs unexpectedly. This observation is in harmony with the findings of several earlier workers, who used a much cruder method of study—titrating the alkalinity of the blood directly, with tartaric acid and litmus paper. In 1878, Canard¹² noted that the alkalinity of the blood is increased following digestion and after ingestion of alkali, decreased, following the ingestion of large amounts of acid. In 1879, Lepine¹³ reported a decreased alkalinity in chronic nephritis, gastric ulcer, diabetes mellitus, and the anemias, and in 1888 von Jaksch,¹⁴ as the result of an extensive investigation, concluded that there is decreased alkalinity of the blood in every febrile process, that the decrease is constant in uremia, diseases of the liver which result in the destruction of tissue, and in the anemias.

Later, Palmer and Henderson¹⁵ studied the acid and ammonia excretion in various nephropathies and noted a decrease in the total titratable acidity of the urine, most pronounced in late glomerular disease, yet also to be observed in the early glomerular and in the degenerative processes. They noted that the decrease was invariably due to an ammonia deficit, just as Adler and Blake¹⁶ had observed that the amount of base excreted in the urine of dogs fed hydrochloric acid followed, in general, the variations in the amount of ammonia. Palmer and Henderson¹⁷ concluded, therefore, that the true regulator of urinary acidity is to be found in the production of ammonia, a process which is "not always correlated with the other regulatory processes of the kidney." The regulation of the hydrogen ion concentration of the blood, they believed to depend almost entirely on the acid excretion.

9 Hoesslin, V. Ueber die Abhängigkeit der Albuminurie vom Sauregrad des Urin und über den Einfluss der Alkalizufuhr auf Azidität, Albuminurie, Diurese und Chloridausscheidung sowie auf das Harnammoniak, *Deutsch Arch f klin Med* **105** 147, 1912.

10 Sellards, A. W. The Determination of Equilibrium in the Human Body Between Acids and Bases with Especial Reference to Acidosis and Nephropathies, *Bull Johns Hopkins Hosp* **23** 289, 1912.

11 Palmer, W. W., and Henderson, L. J. Clinical Studies on Acid-Base Equilibrium and the Nature of Acidosis, *Arch Int Med* **12** 153 (Aug) 1913.

12 Canard, J. Essai sur l'alcalinité du sang dans l'état de santé et dans quelques maladies, *Thèse II*, Paris, 1878.

13 Lepine, R. Note sur la Détermination de l'alcalinité du Sang chez l'homme, *Gaz med de Par* **12** 149 (March 23) 1878.

14 Von Jaksch, R. Ueber die Alkaleszenz des Blutes bei Krankheiten, *Ztschr f klin Med* **13** 350, 1888.

15 Palmer, W. W., and Henderson, L. J. A Study of the Several Factors of Acid Excretion in Nephritis, *Arch Int Med* **16** 109 (July) 1915.

16 Adler, H. M., and Blake, G. The Retention of Alkali by the Kidney, with Special Reference to Acidosis, *Arch Int Med* **7** 479 (April) 1911.

17 Henderson, L. J., and Palmer, W. W. Intensity of Urinary Acidity in Normal and Pathological Conditions, *J Biol Chem* **13** 393, 1913.

PHOSPHATE RETENTION AND RENAL FUNCTION

That acidosis may at times be due specifically to retention of acid phosphate is shown by the work of Greenwald,¹⁸ Marriott and Howland,¹⁹ Feigl,²⁰ Denis and Minot²¹ and others. Greenwald found that the acid soluble phosphorus in nephropathies is increased roughly parallel with the nonprotein nitrogen, while the careful work of Denis and Minot showed a retention of inorganic phosphate by about 65 per cent of the seventy nephropathic individuals studied, reaching ten times the normal value in fatal cases and, in general, closely following the condition of the patient. Marriott and Howland found the inorganic phosphates usually slightly increased in marked renal disease, though death occurred a number of times in such cases, without any increase of phosphorus and without any evidence of acidosis. In certain instances the phosphoric acid was found to be combined with twice as much of the available base as was the carbonic acid, whereas in normal conditions the base combined with phosphoric acid is only from one-tenth to one-fifteenth of that combined with carbonic acid. In mild cases in which the nitrogen retention and the phenolsulphonephthalein elimination were not markedly affected, no phosphate retention was observed.

The excretion of acid phosphate by the normal kidney is stimulated, apparently, in all conditions in which acid tends to accumulate in the body fluids. Thus, Fitz, Alsberg and Henderson²² and later, Underhill and Bogert²³ found an increased elimination of phosphates in rabbits fed with hydrochloric acid. Underhill and Bogert²⁴ also noted that diets producing acid urines in these animals increased the elimination of phosphates through the kidney, while diets producing alkaline urines forced a greater elimination by gut, an observation that has been made on a great variety of animals by other workers and which

18 Greenwald, I. The Estimation of Lipoid and Acid Soluble Phosphorus in Small Amounts of Serum, *J Biol Chem* **21** 29, 1915

19 Marriott, W. McK., and Howland, J. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* **18** 708 (Dec) 1916

20 Feigl, J. Ueber das Vorkommen von Phosphaten im menschlichen Blutserum, *Biochem Ztschr* **83** 218 (Oct) 1917, *Biochemische Untersuchungen über den Einfluss von Marschanstrengungen auf die Zusammensetzung des Blutes*, *ibid* **84** 332 (Dec) 1917

21 Denis, W., and Minot, A. S. Study of Phosphate Retention from the Standpoint of Blood Analysis, *Arch Int Med* **26** 99 (July) 1920

22 Fitz, R., Alsberg, C. L., and Henderson, L. J. On the Intensity of Urinary Acidity in Normal and Pathological Conditions, *Am J Physiol* **18** 113, 1907

23 Underhill, F. P., and Bogert, L. J. Urinary Excretion of Phosphates in the Rabbit, *J Biol Chem* **36** 521 (Dec) 1918

24 Underhill, F. P., and Bogert, L. J. Alterations in the Output of Certain Urinary Constituents as Determined by Changes in the Character of the Diet, *J Biol Chem* **27** 161, 1916

probably forms the basis for the milk treatment of renal insufficiency as it is practiced today. When injected subcutaneously into rabbits Underhill and Bogert recovered from 70 to 100 per cent of the phosphate in the urine and the increment of excretion was no greater with the monobasic than with dibasic and tribasic salts. There was found, however, a wide variation in the ability of individual rabbits to excrete phosphates through the kidney, and it is possible that a similar variation in ability to excrete phosphates occurs among humans, and that the phosphate content of the body fluids of the latter may, in some cases at least, be profoundly modified by the action of the bowel.

The effect of acid phosphate retention on renal function is illustrated by the work of Nagayama,²⁵ who fed to rabbits molecularly equivalent amounts of phosphorus as acid phosphate and as basic phosphate, respectively, and was able to show that the urea excretory activity of the kidney is distinctly depressed after the former, while the latter had no appreciable effect. Sodium bicarbonate in amount markedly increasing the alkalinity of the plasma caused only a slight decrease in this function.

ACID RETENTION AND RENAL FUNCTION

It has long been maintained, notably by Fischer,²⁶ that an abnormal production of acid in the body and its accumulation in the kidney is responsible for the entire symptom complex known as nephritis. To the action of the retained acid on the colloidal structures that make up the kidney are due, in his opinion, the specific morphologic changes, the proteinuria, the production of casts, etc., and on theoretic grounds could as well be initiated by retention of alkali. Newburgh,²⁷ and Newburgh and Squier,²⁸ also state that they have been able to reproduce in the rabbit all the anatomic changes characteristic of the chronic interstitial nephropathy in man, merely by feeding protein in amounts sufficient to increase the urinary nitrogen from 2 to 300 per cent. They, however, made no attempt to correlate their findings with any specific product of protein metabolism, so that it cannot be said whether the increased acid production that must result from such diets was or was not a causative factor.

Of the conditions that govern the excretion of acid by the kidney, little is known. If, as stated by Henderson, this organ is the first line of defense against an accumulation in the body fluids of acid or alkaline

²⁵ Nagayama, T. The Urea Excreting Activity of the Kidney and Phosphate Excretion, *Am J Physiol* **51** 449 (April) 1920.

²⁶ Fischer, M. H. Nephritis, 1912, Ed. 1, New York, John Wiley Sons.

²⁷ Newburgh, L. H. The Production of Bright's Disease by Feeding High Protein Diets, *Arch Int Med* **24** 359 (Oct.) 1919.

²⁸ Newburgh, L. H., and Squier, T. L. High Protein Diets and Arteriosclerosis in Rabbits, A Preliminary Report, *Arch Int Med* **26** 38 (July) 1920.

substances beyond the physiologic optimum, the first indication of its functional lag should, it seems, be found in the acid or alkali binding power of the blood

The acid binding power of the blood, for convenience designated "oxydesis," may be altered by processes occurring without, as well as within the kidney. In the early stages of diabetes mellitus, for example, oxydesis is definitely increased, and according to Michaelis²⁹ and to Menten,³⁰ the H ion concentration of the serum is lowered, while in the later stages, when there is considerable ketone formation, oxydesis is notably decreased, and, according to the same observers, the H ion concentration rises. This may be explained, perhaps, entirely by variations in the ratio of ammonia to acid formed, or it may be due to a preferential retention by the kidney of the stronger fixed bases, the complete elimination in the early stages of acid ammonium salts and later their gradual accumulation because of renal lag.

Since the H ion concentration of the blood depends on the ratio of acid to alkali, the determination of the alkali reserve, indirectly by measuring the bicarbonate bound carbon dioxide of the plasma, or directly by one of the various forms of alkalimetry, cannot serve as an infallible index of acidosis or alkalosis. Thus, Henderson and Haggard,³¹ Van Slyke,³² and Henderson, Haggard and Coburn³³ describe nine theoretically possible combinations of acidosis, alkalosis and normality, by the plasma bicarbonate index, with a high, low and normal alkali reserve, several of which they have clinically observed in conditions where occur such abnormalities of respiration as hyperpnoea and acapnia.

The combination of carbonic acid deficiency and high alkali reserve, we ourselves have observed in diabetic coma of the rapidly advancing type, the oxydesis here being moderately decreased, normal or actually increased, in the face of a plasma bicarbonate content always below twenty volumes per cent. In the nephropathies, however, except when uremia or cardiac decompensation impends, there are, as a rule, no respiratory complications and there is no increased production of acid or alkali. An interesting exception is a condition designated paroxysmal

29 Michaelis, L. Die Wasserstoffionen Konzentration, Berlin, 1914

30 Menten, M. L. The Alkalinity of the Blood in Malignancy and Other Pathological Conditions, Together with Observations on the Relation of the Alkalinity of the Blood to Barometric Pressure, *J. Cancer Res.* **2** 179 (April) 1917

31 Henderson, Y., and Haggard, H. W. Hematorespiratory Functions, *J. Biol. Chem.* **39** 163 (Aug.) 1919, **43** 3, 15 (Aug.) 1920, **47** 421 (July) 1921

32 Van Slyke, D. D. Studies in Acidosis, Normal and Abnormal Variations in Acid-Base Balance of Blood, *J. Biol. Chem.* **48** 153 (Sept.) 1921

33 Henderson, Y., Haggard, H. W., and Coburn, R. C. The Therapeutic Use of Carbon Dioxide after Anesthesia and Operation, *J. A. M. A.* **74** 783 (March 20) 1920

dyspnea or "renal asthma," in which there is a nocturnal anaphylactoid suppression of urine with profound dyspnea, superimposed on what could otherwise be diagnosed a chronic interstitial nephropathy

Whatever be the significance of an increase in the acid fixing power of the blood, a decrease, whether it occur in a nephropathy, in anemia, diabetes mellitus, inanition, ileus, pneumonia or gastric ulcer, and whether it exist as cause or effect thereof, must with great frequency, if not always, be associated with a lag or impairment of renal function. That it is a measure of such impairment cannot be affirmed, for, as was previously stated, it is possible that in a chronic nephropathy the resorptive activity of the bowel may greatly increase, and measurably subserve the function of the kidney

THE ALKALIMETRY OF WHOLE BLOOD

The acid binding power, or oxydesis, of whole blood may be determined as described in the first paper of this series and for the purpose of this investigation represents the greatest amount of hundredth normal hydrochloric acid that can be added to a unit volume of oxalated whole blood without clumping the erythrocytes. For convenience the method is here repeated

Ten clean dry test tubes are set up in a rack. To the first is added 9 cc of an 0.85 per cent salt solution (Merck's blue label sodium chlorid dissolved in freshly distilled water) and 1 cc whole, fresh oxalated blood. A 1 cc differential bacteriologic pipet may be used for the purpose. The blood is mixed with the saline by blowing through the pipet, and froth is avoided by always keeping the tip of the pipet below the surface of the liquid. One cubic centimeter of the diluted blood is then carefully placed in the bottom of each tube, avoiding the sides, and starting on the left, hundredth normal hydrochloric acid containing 0.85 per cent chemically pure sodium chlorid is added with a 2 cc differential pipet, starting with 0.7 cc, and increasing the amount by 0.05 cc with each tube. The tip of the pipet should be poised about 2 inches above the surface of the fluid, to insure rapid diffusion of the acid, which should be dropped directly into the blood and not be touched off on the glass. The tube, once charged, should be shaken immediately, and the row not disturbed until the corpuscles have settled. The last tube which shows the erythrocytes sharply settled in the center without any hemolysis in the supernatant liquid represents the oxydetic value of the blood in question.

The blood should be collected not less than three hours after ingestion of food, in 1 ounce salt mouth bottles, to which 1 cc of a 1 per cent solution of recrystallized, chemically pure sodium oxalate has been added and evaporated to dryness. This amount is sufficient for 10 cc blood, which should be swirled around the bottle immediately on collection. Failure to observe this precaution will result in more or less agglutination of the corpuscles such as always occurs previous to coagulation (blood containing no anticoagulant may be used if one is in a position to dilute it immediately with nine volumes of physiologic solution of sodium chlorid). The syringe and needle should be dry and clean and the blood should be used immediately or placed in a good icebox, where it will keep for twenty-four hours. It should be brought to room temperature before measuring.

Whether the figure obtained in this way represents accurately the buffer content or tampon power of the blood for acid, cannot be stated. It is not known, for example, to what extent the blood-proteins are

available to physiologically fix acid, whether this fixation is a stoichiometric one or whether, as MacLeod ³⁴ states, it is conditioned by the H ion concentration of the blood and becomes greater as the latter increases. The figures obtained will also vary because of differences in calibration of glassware, standardization of acid and, perhaps, a personal factor. The absolute oxydetic values are, however, of little clinical importance. If the same acid and the same pipet be used for the samples of blood that it is desired to compare, it will be found that the amount of acid that can be added to a unit volume of normal blood without clumping the erythrocytes is, for practical purposes, a constant.

Fifty individuals, for example, ranging in age from 19 to 52 years and whose blood and urine were found to be normal, showed an acid fixing power of from 8.5 to 9.5 c.c. of hundredth normal hydrochloric acid per 1 c.c. of whole oxalated blood. Forty-eight of these gave a figure of 9.0, one, 8.5 and one, 9.5, three hours after ingestion of food. Whether a figure below 9.0 consistently indicates a nephropathy or a low renal reserve is the object of this study, and during the past two years, alkalimetry was performed on all patients whose blood and urinary findings suggested a nephropathy and for comparison in many cases in which other diagnoses had been made.

OXYDESIS IN THE NEPHROPATHIES

The nephropathies of vascular origin were, for the purpose of this study, grouped according to the amount of nitrogen retention shown upon first examination. Group I comprised those patients in whom hypertension was the sole finding. Group II showed in addition to hypertension, a retention of nitrogen, and Group III showed hypertension, nitrogen retention and fixation of the specific gravity of the urine. None of the patients of the last group were alive six months after the date of examination. That the parenchymal involvement in these cases was minimal is assumed because there was no history of edema, and none was ever observed.

The nephropathies that were deemed to be predominantly parenchymal in type were, for fault of a better classification, simply regarded as early or late cases, forming Groups IV and V, respectively. Nearly all the patients in these groups had more or less edema, their systolic blood pressures were, as a rule, not high and they were, on an average, much younger than the patients of Groups I, II, and III.

Group VI comprised individuals on whom a definite diagnosis of nephropathy could not be made, in spite of proteinuria, edema or other suggestive symptoms.

³⁴ MacLeod, J. J. R. *Physiology and Biochemistry in Modern Medicine*, Ed. 3, 1920, St. Louis, C. V. Mosby Co., p. 41.

Group VII was composed of what were considered primary cardiac cases characterized by dyspnoea with cyanosis, feeble irregular pulse, subnormal blood pressure and minimal renal involvement

The nonprotein nitrogen was determined by the tungstic acid precipitation method of Folin and Wu,³⁵ and in the same filtrate the chlorids were titrated by the Volhard method adapted thereto by Rieger³⁶ The bicarbonate bound carbon dioxid was determined by the gasometric method of Van Slyke³⁷

DISCUSSION OF RESULTS

Analysis of Tables 1, 2 and 3 reveals little tendency toward accumulation of acid in the nephropathies of vascular type, until a few months before death, when oxydesis may be definitely decreased These patients do not, as a rule, die of acidosis, nor uremia, but of heart failure and although the nonprotein nitrogen of the blood increases steadily up to hundreds of milligrams per hundred cubic centimeters, the phenolsulphonephthalein excretion drops to zero, and the blood chlorids maintain a high level, oxydesis, in the last few days of life, may increase Patients M D and C S in Group III show this tendency to a minor degree, while patient 7,634, Group VII, shows it markedly—oxydesis in the latter instance having been 105 at the time of death This patient was transferred from the class of vascular nephropathies to that of predominant cardiac disease, because of falling blood pressure, and oxydesis rose from 80 to 105, within four months

Patients with marked cardiac involvement have not as a rule shown low oxydesis and the advanced cases cited in Group VII show an acid fixing ability definitely above normal This is possibly due to mobilization in the blood stream of alkali to equilibrate the carbonic acid retained through dyspnea

In the diffuse nephropathies forming Groups IV and V oxydesis is definitely decreased from the onset, acid being retained along with salt, and less constantly, water, before there is any retention of non-protein nitrogen or phenolsulphonephthalein The low figures obtained in patients D R H -S and H H -N, both for oxydesis and blood bicarbonate carbon dioxid, and in both instances within a few hours of death, indicated that they died in acidosis, but that does not mean that they died of acidosis, for D R H -D showed the same low figures two months before death, and D R H -S never had an oxydesis higher than

³⁵ Folin, O., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919

³⁶ Rieger, J B. The Estimation of Chlorids in Whole Blood, *J Lab & Clin M* **6** 44 (Oct) 1920

³⁷ Van Slyke, D D. A Method for the Determination of Carbon Dioxid and Carbonates in Solution, *J Biol Chem* **30** 347, 1917

TABLE 1—Group I Hypertension

Case H H-P	Age	Blood Pressure	Non- protein Nitro- gen	Phenol sul- phone phthal- ein	Oxydosis	Plasma		Whole Blood Chlorids	Urine			Remarks
						Bicar- bonate Carbon Dioxid	Sp Gr		Protein s p t	Sediment		
	12	250-170	28	90	90	68		462			None	Probably the acute interstitial nephritis of Councilman
6110	52	280-140	30	45	90	55		453	1 005-1 022	s p t	Occ hyaline cast	Probable duration 8 years
7869	33	165-110	27	85	90	58		480	1 010-1 032	None	None	Duration less than 1 year
7283	51	300-170	29		90	.			1 012-1 030	s p t	Occ casts and r b c	Symptoms began 1 year ago
8654	50	260-120	27	70	90	61		450	1 005-1 012	s p t	Occ cast	Duration more than 5 years

TABLE 2—Group II Hypertension with Retention of Nitrogen

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenol-sulphone-phthal-ein	Oxydosis	Plasma		Whole Blood Chlorids	Urine			Remarks
						Bicar-bonate Carbon Dioxid	Sp Gr		Protein	Sediment		
6668	49	202-130	40	20	90	54	1 008-1 022	453	s p t	None	Duration at least 2 years, no nyctaluria	
8262	66	160-90	39	60	85	55	1 010-1 020	450	None	Occ hyaline cast	Sole symptom, nyctaluria 1 2 years	
8120	49	250-150	34	45	80	58	1 005-1 012	460	s p t	Occ hyaline case	Duration less than 4 years marked arteriosclerosis	
8924	67	230-100	37	75	90	57	1 005-1 016		s p t	Rare hyaline casts	Senile myocarditis, arterio sclerosis	
1402	49	202-130	34	40	85	60	1 012-1 028	472	s p t	Rare cast	Blood pressure above 150 sys-tolic for 10 years	

TABLE 3—GROUP III HYPERTENSION, NITROGEN RETENTION AND FIXATION OF URINARY SPECIFIC GRAVITY

Case	Age	Blood Pressure	Non protein Nitro gen	Phenol sul phone phthal ein	Oxydesis	Plasma bicarbonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp	Gr	Sediment	
7770	50	235-135	63	15	60	42	555	1 018	1 020	Many casts	Died in 3 months, heart failure
8629	67	240-135	75	20	70	40	570	1 008-1 010		Frequent casts	Died in 1 month, heart failure
8797	51	260-165	42	68	65	45	513	1 020-1 022		Many casts	Died in 3 months, uremic coma
O McD	50	260 150	75		75			1 010 1 011		Occasional casts	Orthopnea, irregular cardiac rhythm, died in 6 months
9253	50	300 160	45	55	75	52	525	1 018 1 022		Occasional casts	Irregular cardiac rhythm, alive 1 month later
M D	48	180-0	150	0	80	68	547	1 009 1 011		Frequent hyaline casts	Died in 3 hours, heart regular to end, pendant edema, aortic disease
C S	47	180 120	275		85	72	530	1 012			Died in 1 hour, no edema, heart regular

TABLE 4—GROUP IV EARLY DIFFUSE NEPHROPATHIES

Case	Age	Blood Pressure	Non protein Nitro gen	Phenol sul phone phthal ein	Oxydesis	Plasma bicarbonate Carbon Dioxid	Whole Blood Chlorids	Urine			Remarks
								Sp	Gr	Sediment	
D R H-B	16	118-75	28		80	51 2	530	1 022		None	Edema of feet and ankles, erythema nodosum
		140-95	38	15	65	57 4	557	1 012 1 015		Many hyaline and granular casts	Acute nephritis with recovery in 1 month, general edema of face, arms and hands
7712	36	115-75	34	46	70	48 1	555	1 022 1 025		Occ hyaline casts, frequent r b c	Severe secondary anemia, edema of legs, enteritis
9099	20	129-80	29	60	80	62 2	519	1 028		None	Malaise, lassitude, sole com plant
8629	19	105 85	28		75			1 032		Considerable blood, no casts	Beginning of an acute hemorrhagic nephritis, early pulmonary tuberculosis

TABLE 5—GROUP V CHRONIC DIFFUSE NEPHROPATHIES

Case	Age	Blood Pressure	Non-protein Nitrogen	Phenolphthalein	Oxydosis	Blood Bicarbonate Carbon Dioxide	Whole Blood Chlorids	Urine			Remarks
								Sp	Gr	Sediment	
5308	42	132-100	35	40	70	53.0	510	1.025-1.030	++	Frequent hyaline casts	Edema of feet for 2 years
7382	33	124-80	42	75	60	42.3	575	1.003-1.010	++	Considerable pus, Occ casts	Pyonephrosis edema of face and extremities for 1 year
7382	5 months later	130-85	35		60	48.7	553	1.001-1.015	++	Much pus	Had been on low nitrogen and low salt diet
H H N	48		160	0	40	12.5			++++		Moribund, necropsy large white kidneys
6302	42	122-70	66	20	55			1.005-1.015	++++	Waxy, fatty epithelial casts	Amyloid disease, persistent slight edema 3 years
6302	6 months later		46		50	35.6			++++		Died in 3 months
D R H K	28	200-100	41		70	55.0	500	1.020-1.028	++++	Many hyaline and granular casts	Uremic convulsion with recovery in 1 month
D R H D	26	155-100	95	25	45	16.3	545	1.015-1.020	++++	Many hyaline and granular casts	General anasarca died 2 months later, necropsy, large white kidneys
3159	16	125-80	32	50	80	66.5	550	1.010-1.020	+++	Tubular casts frequent	Four years duration, no localized edema, pasty appearance
D R H R	35	132-90	33		80	55.4	505	1.006-1.026	+++	Few granular casts	Edema of legs, third admission to hospital in 1 year
D R H S	40	185-115	55	5	45	15.6	582		++++	Many granular casts	Died in 1 hour, necropsy large white kidneys

TABLE 6—GROUP VI RENAL DISEASE SUSPECTED

Case	Age	Blood Pressure	Non protein Nitrogen	Phenol sulphone phthal- ein	Oxydesis	Blood Bicarbonate Carbon Dioxide	Whole Blood Chlorids	Urine		Remarks
								Sp	Gr	
8600	19		28		75	47.5	478	1.022	++	Suspected mediastinal tumor, edema of face and neck, prominent thoracic veins
8760	34	130-84	25		80		462	1.030	++	Attacks of transient, unilateral amaurosis
8622	27	120 80	28	55	80	72.4	470	1.020	+	Diffuse edema of arms and hands, urticaria
9061	42	118 85	30	72	75	52.2	505	1.005	+	Furunculosis, sole complaint, temperature 99.6, beginning hemorrhagic nephritis
8231 J F, nurse	2- 36	128-80 120 84	27 27	80	80 80	68.3 66.5	495 452	1.010-1.030 1.028	++ +	Mild rise, lassitude, pallor
7602	37	98 70	32	74	80	60.2	461	1.030	0	No complaint, frequent puffiness of lower eyelids
8641	45	175 110	30		75			1.008-1.025	0	Strong appearing mechanic, easily fatigued, nocturia II, 7-8 years
8645	17	130-90	29	78	85			1.010-1.018	+	Subacute arthritis, shortness of breath
										Feet swollen for several years, headache, backache, lassitude

TABLE 7—GROUP VII PREDOMINANT CARDIAC DISEASE

Case	Age	Blood Pressure	Non protein Nitrogen	Phenol-sulphone phthal- ein	Oxydesis	Blood Bicarbonate Carbon Dioxide	Whole Blood Chlorids	Urine		Remarks
								Sp	Gr	
9082	54		32	77	100	84		1.020-1.030	+	Mitral stenosis, pulse 128, irregular, no edema, cyanosis
8374	55		55	82	100	78		1.028	++	Pendant edema, dyspnea, cyanosis
7634	57	160-105	50		85	72		1.030	++	Heart sounds weak, rales throughout chest
7634	5 weeks later	160-90	37		80			1.030	+++	Orthopnea, pulse 100
7634	4 months later	120 90	40		105	86	452	1.018	+	Auricular fibrillation, death in 3 days, cyanosis
7223	60		37	75	105	82			+++	Auricular fibrillation, pendant edema, dyspnea, cyanosis

50 or a bicarbonate carbon dioxide higher than twenty-four volumes per cent during his entire stay of one month in the hospital. At necropsy each of these patients showed bilateral large white kidneys.

Finally, there is a large group of patients whose symptoms suggest renal disease, yet in whom the sole evidence of functional impairment is decreased oxydesis. Some of these are included in Group VI. Nearly all show proteinuria, one or two show beginning retention of chlorids, and three or four show a slight edema.

An oxydetic value below 9 c c hundredth normal hydrochloric acid per cubic centimeter blood seems, then, to be an early and constant sign of renal insufficiency, and in all likelihood is due to parenchymal disease. Retention of acid in the diffuse nephropathies apparently precedes the retention of salt and water and is closely related thereto, while the retention of nonprotein nitrogen apparently does not occur until secondary contraction has begun, or in the acute cases, when there is marked oliguresis.

By the same token, the retention of nonprotein nitrogen is the earliest sign of insufficiency in the vascular type of nephropathy—the primarily contracted kidney, but owing to the great glomerular reserve of the organ, retention of acid, chlorids and water does not occur until very late in the disease.

Given, then, hypertension, breathlessness and edema, alone or in association, oxydesis should serve as a gage of the distribution of disease between the vascular bed and parenchyma of the kidney, and in the later stages, as a relative measure of cardiac and renal sufficiency. Thus a figure of 75 or above, with the symptoms mentioned, would mean predominant vascular disease, while lower figures would indicate predominant parenchymal disease. A figure of 85 or more, together with breathlessness, would be taken as an indication of impending heart failure.

The occurrence of decreased oxydesis in conjunction with such vague symptoms as malaise, lassitude, pallor, slight proteinuria or transient localized edemas, alone or in combination, demonstrates the possibilities of alkalimetry in the diagnosis of early diffuse nephropathies.

Indeed, in our experience, a decreased oxydesis is the earliest and most constant sign of renal insufficiency. What may be its exact significance cannot be stated. The work of Nash and Benedict³⁸ indicates that the kidney is a seat of ammonia formation, and Palmer and Henderson have shown quite conclusively that there is, in the various nephropathies, a deficit in the output of urinary ammonia, bound with fixed acid. That certain ammonium salts retained by a damaged

38 Nash, T. P. Jr., and Benedict, S. R. The Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, *J. Biol. Chem.* **48** 463 (Oct.) 1921.

kidney can function as acid in degree sufficient to appreciably lower the alkali reserve, is exceedingly doubtful. It is more logical to argue that the lesion which damages the acid excreting function of the kidney damages the ammonia producing function as well.

SUMMARY

1 The greatest amount of acid that may be added to a unit volume of whole blood without agglutinating its erythrocytes is taken as the acid binding value of that blood. It is designated "oxydesis."

2 Oxydesis in health and in the postabsorptive state is for practical purposes a constant. For 1 c.c. whole blood, oxalated as described, it is approximately equivalent to 9 c.c. hundredth normal alkali.

3 Oxydesis, below ninety (0.9 c.c. hundredth normal hydrochloric acid per 0.1 c.c. blood) appears to be an early and constant sign of renal insufficiency when due to a glomerular lesion.

4 In the diffuse nephropathies oxydesis is definitely increased before there is retention of water, chlorids, or phenolsulphonephthalein and long before there is nitrogen retention.

5 In the degenerative vascular nephropathies, there is retention of nitrogen before there is retention of chlorids, water or phenolsulphonephthalein, and oxydesis is not definitely decreased until the late stages.

6 In cardiorenal disease, with preponderant cardiac involvement, oxydesis is normal, and in the late stages increased.

7 In cardiorenal disease, oxydesis serves as a rough gauge of the relative involvement of heart and kidney.

8 Decreased oxydesis signifies a decreased alkali reserve, either because of an accumulation of acid, deficient production of ammonia or both.

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INTERPRETATION OF THE WASSERMANN REACTION

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One hesitates in the present day to write on a subject which has been so ably and fully discussed as the Wassermann reaction,¹ and to add to a literature already large. During a clinical experience of about seven years, however, in which Wassermann tests have been made as a routine measure in our medical examinations, we have had an unusual opportunity of seeing the value of the test in clinical medicine, and since our tests have been made with both sensitive and coarse (or insensitive) methods simultaneously, we have also had an opportunity to observe the value and dependability of several technics. We wish, therefore, to present briefly data and conclusions gained from more than 50,000 tests on more than 10,000 specimens of blood taken from patients the majority of whom we examined ourselves. Our Wassermann technic has been changed in some of its details from time to time. For this reason, some of the tabulations reported are based on only fifteen hundred consecutive medical cases in which the exact methods to be described have been used. All of the patients from whom this data was obtained were examined carefully, and in our examinations we endeavored to disclose and record every abnormality which could be brought to light by history, physical examination, special examinations, clinical pathology and roentgenology.

I may say at the outset that this paper presents nothing new to the careful serologist nor internist. It is rather a compilation of statistics for the purpose of comparing clinical and serologic findings. It is written partly with a hope of helping restore confidence in the Wassermann reaction in the minds of physicians who may have lost respect for the test on account of contradictory reports given them by serologists who have used widely differing methods.

1 It hardly comes within the scope of this paper to cite the many brilliant researches which have led to our present knowledge of serology in its relationship to the diagnosis and treatment of syphilis. For a review of this literature the reader is referred to the monographs of Noguchi, Craig, Kolmer, etc.

DEVELOPMENT OF THE WASSERMANN TECHNIC

In the early days of Wassermann work, opinions were in harmony concerning the significance of a positive reaction and the relative frequency with which positive reactions were obtained in the different stages of syphilis. It was conceded by the majority of observers that a four plus reaction was given by few, if any, diseases other than syphilis, that a negative reaction did not exclude a diagnosis of syphilis, that the vast majority of secondary cases gave positive reactions, but that a smaller proportion of the primary, tertiary and so-called latent cases gave positive reactions.

The technic as originally used was relatively crude and insensitive. The disease had to be moderately active in order to give a positive reaction. For this reason the Wassermann test failed where it was most needed—that is, in disclosing the disease in late cases in which the symptoms were not well defined.

A number of unique methods were devised for making the test more sensitive, thereby making it possible to obtain a larger proportion of positive reactions in the less active cases. The more important of the measures were the use of reinforced antigens, the use of one unit of complement instead of two units, and finally, incubation at icebox temperature in place of incubation at a temperature of 38 C. These modifications made it possible to carry out a Wassermann reaction which was far more delicate than tests carried out by the method as originally described. The great advantage derived from the modifications was a test which would give positive reactions in the vast majority of cases of syphilis whether early or late. It was offset by a serious disadvantage—namely, unreliability. With the modified method, positive reactions were obtained in a certain proportion of patients who did not have demonstrable syphilis.

At the present time one or all of the modifications mentioned are used in some laboratories, while in others the test used is not materially different from the original Wassermann test. The result is that in some laboratories a method is used which is much more sensitive than that used in other laboratories. Unfortunately, results are reported by the majority of laboratories in the same symbols as those used early in Wassermann work—namely, negative, one plus, two plus, three plus and four plus, regardless of whether the test used is comparatively insensitive, as was the original Wassermann test, or exceedingly sensitive. As a result, practitioners at the present time may send blood to several laboratories and receive a different report from each.

Disagreements of this sort have caused a plea from all quarters for a standard test which might make it possible for all laboratories to obtain uniform results. Such disagreements have also induced a prevalent

belief among physicians in many localities that the Wassermann test is almost worthless, that it is merely a symptom of disease, and an unreliable one at that. What is to blame for this situation?

In my opinion it is not due so much to the use of the unique improvements in technic which have made the test more sensitive, nor to the lack of a standard test, as to the fact that all Wassermann reactions, whether obtained by sensitive or insensitive methods, are reported in the same technical and inadequate terms—one plus, two plus, three plus and four plus. Some of the discrepancies would be avoided if the reports were made in plain English words which would have the same meaning to all serologists and to all physicians, such, for example, as doubtful, weakly positive and strongly positive. A result labeled strongly positive would surely never be reported or accepted on the basis of a four plus reaction obtained by the more sensitive methods.

The ideal Wassermann reaction, unfortunately, can never be realized through the use of any one single test, no matter what technic is used. An ideal Wassermann test would be one sensitive enough to come out

TABLE 1—DESCRIPTION OF TESTS 1 TO 5

	Test 1	Test 2	Test 3	Test 4	Test 5
Antigen	Cholesterinized 0.1%	Cholesterinized 0.2%	Cholesterinized 0.2%	Acetone insoluble	Alcoholic extract
Complement	1 unit	1 unit	2 units	2 units	2 units
Sensitiveness of test	Extremely sensitive	Very sensitive	Moderately sensitive	Moderately sensitive	Moderately sensitive

positive in every case of syphilis, whether early or late, and, at the same time, so insensitive as to never give a false positive. Such a test is theoretically and practically impossible. A test sensitive enough to come out positive almost invariably in patients with late syphilis is, of necessity, so sensitive that it will come out positive in a certain proportion of patients not afflicted with syphilis. As a practical alternative, I have used a five tube test. Two of the tubes are sensitive enough to give a positive result in the great majority of patients with syphilis, whether early or late, two tubes are so coarse, or insensitive, as virtually never to give a false positive result, and one tube is intermediate.

METHOD

My plan for setting up Wassermann tests may be criticized as being unnecessarily complex. At the same time, it has given me an unusual opportunity of observing the clinical significance of several types of technic.

Briefly the method is as follows. Tube 1 contains cholesterinized antigen (0.4 per cent) with one unit of complement. Tube 2 contains

cholesterinized antigen (0.2 per cent) with one unit of complement Tube 3 contains cholesterinized antigen (0.2 per cent) with two units of complement Tube 4 contains acetone insoluble antigen (noncholesterinized) with two units of complement Tube 5 contains alcoholic extract (noncholesterinized) with two units of complement

From one-fourth to one-fifth of a slightly anticomplementary quantity of antigen was used in tube 1 and from one-fifth to one-eighth (this has been changed from time to time) in tubes 2, 3, 4 and 5, 0.05 c.c. of inactivated patient's serum was used in all tubes, total volume of tests 1.25 c.c., incubation icewater bath at 8 C one hour, sheep system²

While this method is rather complex it presents one real advantage, namely, its scope. It includes two tests which are exceedingly sensitive, two tests which are moderately coarse, and one intermediate test

THE COMPARATIVE DELICACY OF DIFFERENT WASSERMANN METHODS

The comparative delicacy of the five tests described is shown in Tables 2 and 3. In these two tables, however, two tubes were added to the five ordinarily used. The technic used in these two additional tests (Tests 6 and 7) was the same, respectively, as that used in Tubes 4 and 5, except that they were incubated at 38 C instead of 8 C, as were tubes 1, 2, 3, 4 and 5. Two known positive specific bloods were titrated down with the technic of each test (Tests 1 to 7) starting with 0.1 c.c. of blood serum and ending with $\frac{1}{4000}$ c.c. By noting the smallest quantity of serum required to give a four plus reaction in each tube one can observe the relative delicacy of each of the seven methods.

Test 7 (Table 2) gave a four plus reaction with $\frac{1}{80}$ c.c. of blood, while approximately one-half this amount, or $\frac{1}{160}$ c.c., was sufficient to give a four plus reaction in tests 4 and 5 (same tests as 5 and 7, except for the use of icewater bath incubation), approximately one-fourth that amount, or $\frac{1}{320}$ c.c., was sufficient to give a four plus reaction in test 3 (same test as 4 and 5, except for the use of cholesterinized antigen), approximately one-eighth this amount, or $\frac{1}{640}$ c.c., was sufficient to give a four plus reaction in test 2 (same as test 3, except for the use of one unit of complement instead of two units), and approximately one-sixteenth this amount, or $\frac{1}{1280}$ c.c., was sufficient to give a four plus reaction with test 1 (same as test 2, except that more antigen and more cholesterolin was used). In other words, the technic used in test 1 was approximately sixteen times as sensitive as that of tests 6 and 7, which have relatively the same delicacy

² Duke, W. W. Ice Water Bath in Complement Fixation for the Wassermann Reaction. A Shortened Technic, *Am J Syph* 5:312 (April) 1921

TABLE 2 — TITRATIONS OF A STRONG POSITIVE BLOOD BY SEVEN DIFFERENT TECHNIQS TO SHOW THEIR COMPARATIVE DELICACY

	Technic 1	Technic 2	Technic 3	Technic 4	Technic 5	Technic 6	Technic 7
Antigen	0.4% C	0.2% C	0.2% C	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized
Complement	1 U	1 U	2 U	2 U	2 U	2 U	2 U
Temp. of fixation	8 C	8 C	8 C	8 C	8 C	37.5 C	37.5 C
Serum, C c							
1 10	4+	4+	4+	4+	4+	4+	1+
1 15	4+	4+	4+	4+	4+	4+	4+
1 20	4+	4+	4+	4+	4+	4+	4+
1 30	4+	4+	4+	4+	4+	4+	4+
1 40	4+	4+	4+	4+	4+	4+	4+
1 60	4+	4+	4+	4+	4+	4+	4+
1 80	4+	4+	4+	4+	4+	4+	4+
1 120	4+	4+	4+	4+	4+	3+	3+
1 160	4+	4+	4+	4+	4+	2+	—
1 240	4+	4+	4+	2+	2+	—	—
1 320	4+	4+	4+	—	—	—	—
1 480	4+	4+	1+	—	—	—	—
1 640	4+	4+	—	—	—	—	—
1 960	4+	3+	—	—	—	—	—
1 1280	4+	2+	—	—	—	—	—
1 1440	2+	1+	—	—	—	—	—
1 1600	1+	—	—	—	—	—	—

TABLE 3 — TITRATIONS OF A STRONG POSITIVE BLOOD BY SEVEN DIFFERENT TECHNIQS TO SHOW THEIR COMPARATIVE DELICACY TECHNIQS DESCRIBED BELOW

	Technic 1	Technic 2	Technic 3	Technic 4	Technic 5	Technic 6	Technic 7
Antigen	0.4% C	0.2% C	0.2% C	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized
Complement	1 U	1 U	2 U	2 U	2 U	2 U	2 U
Temp. of fixation	8 C	8 C	8 C	8 C	8 C	37.5 C	37.5 C
Serum, C c							
1 10	4+	4+	4+	4+	4+	4+	3+
1 15	4+	4+	4+	4+	4+	3+	2+
1 20	4+	4+	4+	4+	4+	1+	1+
1 30	4+	4+	4+	4+	4+	—	—
1 40	4+	4+	4+	4+	4+	—	—
1 60	4+	4+	4+	4+	4+	—	—
1 80	4+	4+	4+	4+	4+	—	—
1 120	4+	4+	4+	3+	3+	—	—
1 160	4+	4+	4+	—	—	—	—
1 240	4+	4+	1+	—	—	—	—
1 320	4+	3+	—	—	—	—	—
1 480	4+	1+	—	—	—	—	—
1 640	2+	—	—	—	—	—	—
1 960	1+	—	—	—	—	—	—
1 1280	—	—	—	—	—	—	—
1 1440	—	—	—	—	—	—	—
1 1600	—	—	—	—	—	—	—

as the original Wassermann. A number of similar titrations with different specimens of blood have shown essentially the same result. With other bloods, however, a much greater difference was frequently encountered between tests 4 and 5, on the one hand, and tests 6 and 7 on the other (where warm water bath fixation was used). Table 3, for example, shows that tests 4 and 5 were about eight times as sensitive as were tests 6 and 7.

One might point out another factor of interest which can be observed in these tables, namely, the relatively small difference in the amounts of serum required to give a four plus and a one plus reaction by each test. Regardless of technic, a four plus reaction was given by little or no more than twice the amount of serum required to give a one plus reaction. The difference, then, between a one plus reaction and a four plus reaction is not great, in fact, a one plus reaction by technics 4, 5, 6 and 7 has much more real significance than a four plus reaction given by technics 1 or 2.

It may be repeated here, that in some laboratories a four plus reaction is reported on the basis of a result obtained by a test as delicate as my tube 1, while in other laboratories a four plus reaction is reported only on the basis of a four plus reaction obtained by a test relatively as coarse as that described for tubes 4 and 5, or, in some laboratories, even as coarse as tubes 6 and 7. So long as this is the case, and results are reported regardless of technic in the same technical terms—one, two, three and four plus, opinions will differ concerning the reactions given by doubtful and weakly positive bloods.

STATISTICS

My statistics are based on a study of patients referred to me for general medical examination. So few were referred because of primary or secondary syphilis that this type of case can virtually be excluded from the tabulations. The statistics are based on a study of miscellaneous chronic medical cases, in 107 per cent of which active syphilis was demonstrable and a very large per cent of these showed involvement of the central nervous system.

To give the Wassermann reaction its proper place in a clinical diagnosis one must know the actual value and significance of a positive reaction and of a negative reaction for the method used. This varies greatly with different methods. Unless one realizes this fact, and understands exactly what his positive and his negative reactions indicate, the Wassermann reaction may be very misleading, as is shown by the data obtained with the different tests as reported in Tables 4 and 5.

Test 1 gave a four plus reaction in 95 per cent of patients in whom syphilis was found clinically. It was from one to three plus in 4 per

cent of the remaining 5 per cent, and negative in less than 1 per cent. In fact, we have on our records only two patients who had syphilis positively proven (and who were not recently treated) who gave a flat negative reaction with test 1. These two patients had very active syphilis, both recovered under treatment but gave persistently negative Wassermann reactions with both blood and spinal fluid. Test 1 gave a four plus reaction in 31.5 per cent of consecutive medical cases with miscellaneous diseases (including syphilis), and in these cases syphilis was found clinically in only 32.2 per cent. The four plus reactions given by this technic were, therefore, false positives in 67.8 per cent of cases. It is quite evident, therefore, that while a negative reaction with test 1 is of great value in the exclusion of syphilis (error

TABLE 4 — PERCENTAGE OF POSITIVE REACTIONS GIVEN BY TESTS 1 TO 5 IN MISCELLANEOUS MEDICAL CASES (INCLUDING SYPHILIS) AND IN PATIENTS WITH SYPHILIS, ALSO THE APPARENT PERCENTAGE OF FALSE POSITIVES

	Test 1	Test 2	Test 3	Test 4	Test 5
4+ reactions in miscellaneous medical cases	31.5%	13.2%	8.5%	6.2%	5.8%
4+ reactions in patients with syphilis	95 %	84 %	75 %	59 %	57 %
Percentage of false positives given by tests	67.8%	34 %	7.3%	Less than 2% (?)	Less than 2% (?)

TABLE 5 — PERCENTAGE OF FALSE POSITIVES GIVEN BY THE FOUR TYPES OF REACTION SHOWN BELOW. THESE PERCENTAGES DIFFER FROM THOSE OF TABLE 4, LINE 3, BUT ARE BELIEVED TO PICTURE MORE CORRECTLY THE ACTUAL VALUE OF THE POSITIVE REACTIONS FOR EACH TEST

Test 1	Test 2	Test 3	Test 4	Test 5	False Positives
4+	—	—	—	—	93.5%
4+	4+	—	—	—	79%
4+	4+	4+	—	—	30%
4+	4+	4+	4+	4+	Less than 2%

very small), a positive reaction is of no value whatever in its positive diagnosis.

At this point, I wish to call attention to a very misleading fact. I stated that more than 67 per cent of the four plus reactions obtained with test 1 were apparently false positives. While this is true, the impression conveyed is incorrect. To know the dependability of a four plus reaction with a given test (for example, test 1) one must not tabulate all cases which give a four plus reaction with that test (including both strongly positive and mildly positive bloods) but must take only such bloods as give a four plus reaction by this technic alone—that is, bloods which are too mildly positive to give a four plus reaction with the less sensitive tests. To repeat for the sake of clear-

ness, it is necessary, in order to determine the actual value of a positive reaction with a given technic (such as that of test 1) to exclude from the tabulations bloods which give strong positive reactions (such as $4 + 4 + 4 + 4 + 4 +$ or $4 + 4 + 4 + - -$, etc., by the five tube test) Conclusions must be drawn only from bloods which give $4 + - - - -$ reactions We have compared bloods which gave this latter type of reaction (namely $4 + - - - -$) with clinical findings in a large series of cases, and, surprising to relate, only 65 per cent of the patients had syphilis which could be demonstrated by other means, in other words, actually 93.5 per cent of the positives of this type were apparently false positives We believe, therefore, that a test so sensitive as that obtained by the use of a 0.4 per cent cholesterinized antigen, with one unit of complement and icewater bath incubation, is absolutely worthless so far as the positive diagnosis of syphilis is concerned A negative reaction, however, is very useful in the exclusion of syphilis

The results obtained with test 2 were much the same as those obtained with test 1 This test came out four plus in 84 per cent of patients who had positively proven syphilis, and in 13.2 per cent of medical patients with miscellaneous diseases (including syphilis) Of this 13.2 per cent, syphilis was found in only 66 per cent The four plus reactions given by test 2, therefore, were false positives in 34 per cent of cases This latter figure also gives an erroneous idea concerning the reliability of a positive reaction with technic 2 As previously stated, the reliability of a test must not be based on a tabulation of all bloods which give a positive reaction with that test but only those which are sufficiently positive to give a positive reaction with that test, in other words, on bloods which give positive reactions with tests 1 and 2 with negative reactions with tests 3, 4 and 5 In bloods of this type (i. e. $4 + 4 + - - -$) syphilis was demonstrated in only 21 per cent—that is, of the positives of this class 79 per cent were apparently false positives Test 2, therefore, in which 0.2 per cent cholesterinized antigen was used with one unit of complement and icewater bath incubation, would appear to be worthless in the positive diagnosis of syphilis A negative reaction with this test is of less value in the exclusion of syphilis than with test 1

The most interesting and also the most misleading statistical facts were obtained through tabulations of test 3 Test 3 came out four plus in 75 per cent of patients who had proven syphilis It came out four plus in 8.5 per cent of miscellaneous medical cases (including syphilis) Of these positives syphilis was found in 92.7 per cent Only 7.3 per cent of positives with test 3, therefore, were false positives The reliability of positives with test 3, however, cannot be based on these statistics While the facts are correct, the impression given by them is most erroneous Of the patients who gave four plus

reactions with tests 1, 2 and 3, with negative reactions with tests 4 and 5 (that is 4 + 4 + 4 + — —) syphilis was demonstrated in only 70 per cent, in other words, of the bloods barely strong enough to give a positive four plus with tests 1, 2 and 3 (that is 4 + 4 + 4 + — —), 30 per cent were false positives. We believe, therefore, that test 3, carried out with cholesterinized antigen (0.2 per cent), two units of complement, and icewater bath fixation, is of no value as a diagnostic test. It appears from the data at hand to be the borderline test which is too sensitive to give reliable positives and too coarse to give dependable negatives.

Tests 4 and 5 came out four plus in only 59 and 57 per cent, respectively, of patients having demonstrable syphilis. They came out negative to three plus in 41 and 43 per cent, respectively, of persons in whom syphilis was demonstrated clinically. In marked contrast with the previous tests, they gave no definitely proven false positives so far as I have been able to determine. I demonstrated the presence of active syphilis through history, physical examination, lumbar puncture or therapeutic test in 98 per cent of patients who gave this type of reaction (namely 4 + 4 + 4 + 4 + 4 +). In the remaining 2 per cent, syphilis was not proven. I must add, however, that this 2 per cent of cases were not adequately examined on account of insufficient time or lack of cooperation on the part of the patient. Tests 4 and 5 in which noncholesterinized antigens were used with two units of complement and icewater bath incubation, appeared to be the most sensitive techniques which could be used if reliable positives were to be obtained. In fact, if I were to alter my technic at the present time, I would, for the sake of dependability, make tests 4 and 5 a little less sensitive. I must admit also that while I stated that four plus reactions in tubes 4 and 5 were almost proof positive of syphilis the actual dependability of these two tests could be more accurately estimated by examination of a group of patients who gave four plus reactions in these two tubes with negatives in tests a little less sensitive. Unfortunately I have no statistics of this sort to tabulate.

FALSE POSITIVE REACTIONS WITH TESTS 1, 2 AND 3

As stated previously, tests 1, 2 and 3 give a surprisingly large number of positive reactions in subjects in whom specific disease could not be demonstrated by other means. In such persons these tests came out positive much more frequently when they were ill and visited a doctor for this reason than when they were tested as candidates to be donors for blood transfusion (apparently healthy persons). It was also observed that false positives of this type were obtained more frequently in patients with goiter (regardless of size and toxicity), extreme ptosis, active tuberculosis, chronic sepsis, hypertension, pernicious anemia, diabetes and atrophic arthritis than in persons who did

not have these diseases. These facts were of only passing interest so that the cases were not tabulated carefully for the purpose of getting accurate statistics. In none of this group of cases which gave false positives with tests 1, 2 and 3, inclusive, but in which syphilis was not demonstrable, were tests 4 and 5 positive.

In Table 6 are recorded twenty-five consecutive cases of tuberculosis (clinically free from syphilis) and twenty-five consecutive cases of late syphilis with the respective Wassermann reactions. It is interesting to contrast the tuberculous cases with their many false positive reactions in the sensitive tubes with the large per cent of strongly positive reactions given by patients with syphilis.

It is of interest to illustrate by titration (Table 7) the large amount of complement fixing body contained in blood obtained from patients having syphilis as compared with the small amount of complement fixing body contained in the blood of nonsyphilitic goiter cases giving false positives with such sensitive tests as 1 and 2. Table 7 presents a comparison of three bloods (A, B and C) taken from patients with syphilis titrated down with the technic of test 1. For comparison are given titrations by the same method of three bloods taken from goiter patients (X, Y and Z) who were clinically free of syphilis but who gave false positives with tests 1 and 2.

The three bloods taken from patients with syphilis gave four plus reactions even when infinitesimal amounts of serum were used. Blood A, for example, gave a four plus reaction with $\frac{1}{6000}$ c c of serum, blood B with $\frac{1}{1500}$ c c, blood C with $\frac{1}{750}$ c c of serum. In contrast with these, each of three goiter cases (X, Y and Z) gave four plus reactions with $\frac{1}{40}$ c c of blood but titrations showed that even as much as $\frac{1}{100}$ c c gave negative results. This table illustrates how trifling is the reaction of a false positive blood as compared with the blood of a patient with syphilis. I have frequently examined patients who have been told that their blood gave a four plus reaction and on titrating we found a mild reaction (such as X, Y and Z) and in diagnostic tests found that they gave four plus reactions with test 1 or tests 1 and 2 with negatives in tests 3, 4 and 5. Positive reports based solely on positive findings with sensitive tests may be very misleading.

It can readily be understood after perusal of Table 7 that the four plus reactions of goiter bloods (X, Y and Z) might be four plus one day and flatly negative the next, if only sensitive tests be used. Patients who have so little complement fixing body in their blood as these might easily have just enough to give a positive reaction one day by a sensitive test and none at all the next day. In fact, I have frequently encountered bloods of this sort. One could judge, however, from these titrations (A, B and C) how difficult it would be for a real case of syphilis having actually a strongly positive test to give a positive reaction

TABLE 6 — WASSERMANN REACTIONS GIVEN BY TWENTY-FIVE CONSECUTIVE CASES EACH OF TUBERCULOSIS AND SYPHILIS

No	Syphilis					Tuberculosis				
	Test 1	Test 2	Test 3	Test 4	Test 5	Test 1	Test 2	Test 3	Test 4	Test 5
1	1+	4+	4+	4+	4+	3+	—	—	—	—
2	4+	4+	4+	3+	1+	—	—	—	—	—
3	4+	4+	4+	4+	4+	1+	—	—	—	—
4	4+	4+	4+	—	—	4+	4+	—	—	—
5	4+	4+	4+	4+	4+	4+	3+	—	—	—
6	4+	1+	4+	4+	4+	—	—	—	—	—
7	4+	4+	4+	4+	4+	4+	4+	4+	—	—
8	4+	4+	4+	4+	4+	4+	—	—	—	—
9	4+	4+	4+	1+	—	—	—	—	—	—
10	4+	4+	2+	—	—	—	—	—	—	—
11	4+	4+	4+	4+	4+	4+	—	—	—	—
12	4+	4+	—	—	—	—	—	—	—	—
13	4+	4+	4+	4+	4+	4+	4+	—	—	—
14	4+	4+	4+	4+	4+	4+	4+	—	—	—
15	4+	—	—	—	—	—	—	—	—	—
16	4+	4+	4+	2+	1+	4+	4+	—	—	—
17	4+	4+	4+	4+	4+	—	—	—	—	—
18	4+	4+	4+	—	—	—	—	—	—	—
19	4+	4+	4+	4+	4+	4+	3+	—	—	—
20	3+	1+	—	—	—	—	—	—	—	—
21	4+	4+	4+	4+	4+	—	—	—	—	—
22	4+	4+	4+	4+	4+	4+	—	—	—	—
23	4+	4+	4+	4+	4+	—	—	—	—	—
24	4+	4+	4+	2+	1+	3+	—	—	—	—
25	4+	4+	3+	—	—	2+	—	—	—	—

TABLE 7—COMPARISON BY TITRATION OF STRONG POSITIVE SPECIFIC BLOODS WITH THOSE OF GOITER PATIENTS WHO GAVE FALSE POSITIVE REACTIONS WITH TEST 1

Strong Positive Serums (Three Syphilitic Cases)				Goiter Cases (With False Positive Reaction in Test 1)			
Serum	A	B	C	Dilution	X	Y	Z
1 10 cc	4+	4+	4+	1 10 cc	4+	4+	4+
1 15 cc	4+	4+	4+	1 15 cc	4+	4+	4+
1 20 cc	4+	4+	4+	1 20 cc	4+	4+	4+
1 30 cc	4+	4+	4+	1 30 cc	4+	4+	4+
1 40 cc	4+	4+	4+	1 40 cc	4+	4+	4+
1 60 cc	4+	4+	4+	1 60 cc	4+	2+	1+
1 80 cc	4+	4+	4+	1 80 cc	2+	—	—
1 120 cc	4+	4+	4+	1 120 cc	—	—	—
1 160 cc	4+	4+	4+	1 160 cc	—	—	—
1 240 cc	4+	4+	4+				
1 320 cc	4+	4+	4+				
1 480 cc	4+	4+	4+				
1 640 cc	4+	4+	4+				
1 960 cc	4+	4+	4+				
1 1280 cc	4+	4+	3+				
1 1500 cc	4+	4+	3+				
1 1750 cc	4+	3+	2+				
1 2000 cc	4+	1+	2+				
1 2500 cc	4+	1+	—				
1 3000 cc	4+	—	—				
1 4500 cc	4+	—	—				
1 6000 cc	4+	—	—				
1 7500 cc	2+	—	—				
1 9000 cc	—	—	—				

one day and a negative reaction the next, (except possibly after the use of alcohol-Craig) for in the ordinary diagnostic test $\frac{1}{20}$ c c or more of blood is usually used. I have never encountered a blood which gave a real positive test (a four plus reaction in all five tubes) which became negative except after weeks or months of time or treatment. It has not been rare in my experience, however, for a four plus in test 1 with negatives in tests 2, 3, 4 and 5, to change after a week or so to a flat negative.

I might also point out (using Table 7 as an example) how needless it is to use in a diagnostic test an amount of serum much greater than about $\frac{1}{20}$ c c when it is possible to devise a technic so delicate that as little as $\frac{1}{6000}$ c c has been known to give a four plus reaction. The use of large amounts of blood serum unfortunately gives rise to sources of error due to anticomplementary bodies, natural antisheep amboceptor, etc. These sources of error are reduced when small quantities of the patient's serum are used in the tests.

THE INTERPRETATION OF POSITIVE, NEGATIVE AND DOUBTFUL REACTIONS

It seems that the nearest one can approach the ideal Wassermann test at present is, first, to employ one or more tests sensitive enough to come out four plus in a great majority of cases of syphilis, second, to employ one or more tests so coarse or insensitive that they will under almost no circumstances give a false positive, third, to employ an intermediate test which is reasonably delicate and reasonably coarse, and which can be observed and taken with a grain of salt. When tests are carried out in this way, clean cut definite information can be gained. Active syphilis can be excluded almost entirely (error very small) if every test comes out flatly negative. Syphilis is almost proven positively if every test results in four plus. Difficulty arises when the delicate tests are positive, and the coarse tests are negative. In this case syphilis is neither proven nor disproven. Such a reaction, according to my experience, must be termed "doubtful" or "suspicious" and had better be excluded from use in diagnosis. The diagnosis of syphilis in patients giving doubtful reactions of this sort is subject to smaller error if based entirely on history, physical examination, lumbar puncture or the therapeutic test.

SERUM TITRATIONS AS A GUIDE IN THERAPY

While in my own work I use the term strongly positive in discussing bloods which give four plus reactions in all five tubes, I realize that in order to determine the real strength of a positive blood and call it actually strongly positive one must titrate (Tables 2 and 3). This is of more value in following the treatment, however, than it is in making a diagnosis.

This paper deals primarily with the Wassermann test as a diagnostic measure. However, I cannot refrain from saying something about the value of serum titrations as a guide to treatment and the inadequacy of a simple diagnostic technic for this purpose. Tables 8 and 9 show how confusing the Wassermann results may be in judging the result of treatment unless titrations are made. I have followed this procedure as a routine for two years in the majority of specific cases under my care and the titrations are shown in Tables 8 and 9 as a typical example.

TABLE 8—WASSERMANN RESULTS OF THE FIVE TUBE TEST IN A PATIENT UNDER TREATMENT FROM APRIL TO MARCH (ELEVEN MONTHS). NOTE ABSENCE OF APPARENT IMPROVEMENT AND COMPARE WITH TITRATION RESULTS MADE SIMULTANEOUSLY SHOWN IN TABLE 9

	April	June	July	Aug	Oct	Jan	Feb	March
0.4% cholesterinized antigen	4+	4+	4+	4+	4+	4+	4+	4+
0.2% cholesterinized antigen	4+	4+	4+	4+	4+	4+	4+	4+
0.2% cholesterinized antigen (2 U complement)	4+	4+	4+	4+	4+	4+	4+	4+
Acetone insoluble	4+	4+	4+	4+	4+	4+	4+	3+
Alcoholic extract	4+	4+	4+	4+	4+	4+	3+	1+

TABLE 9—WASSERMANN TITRATIONS MADE SIMULTANEOUSLY WITH DIAGNOSTIC TESTS SHOWN IN TABLE 8. NOTE MARKED IMPROVEMENT WHICH WAS NOT SHOWN BY THE DIAGNOSTIC REACTIONS

Serum	April	July	Aug	Oct	Jan	Feb	March
1 10 cc	1+	4+	4+	4+	4+	4+	4+
1 15 cc	4+	4+	4+	4+	4+	4+	1+
1 20 cc	4+	4+	4+	4+	4+	4+	—
1 30 cc	4+	4+	4+	4+	4+	4+	—
1 40 cc	4+	4+	4+	4+	4+	4+	—
1 60 cc	4+	4+	4+	4+	4+	4+	—
1 80 cc	4+	1+	4+	4+	4+	4+	—
1 120 cc	4+	4+	4+	4+	4+	3+	—
1 160 cc	4+	4+	4+	4+	4+	1+	—
1 240 cc	4+	4+	4+	4+	4+	—	—
1 320 cc	4+	4+	4+	4+	3+	—	—
1 480 cc	4+	4+	4+	4+	1+	—	—
1 640 cc	4+	4+	4+	2+	—	—	—
1 960 cc	4+	4+	4+	—	—	—	—
1 1280 cc	4+	4+	4+	—	—	—	—
1 1500 cc	4+	4+	2+	—	—	—	+
1 1750 cc	4+	4+	1+	—	—	—	—
1 2000 cc	4+	3+	—	—	—	—	—
1 2500 cc	2+	1+	—	—	—	—	—
1 3000 cc	—	—	—	—	—	—	—
1 4500 cc	—	—	—	—	—	—	—

Table 8 shows Wassermann results obtained with the five tube diagnostic test previously described used on a patient under treatment at different dates (April to March). During this period of eleven months the patient was under antisppecific treatment and improved clinically. It can be noted, however, that during this entire period tests 1, 2 and 3 were all unchanged. They were four plus in the beginning of treatment and four plus at the end of this period. Test 4 showed no change for eleven months when it became three plus instead of four plus.

Test 5 showed no change for ten months when it became less strongly positive. Should one have this chart alone he might wonder why this patient had not shown more improvement serologically during this period. Was he a Wassermann-fast case, an incurable cerebral case, or what? A different impression is gained from Table 9 which gives the result of serum titrations carried out simultaneously with the diagnostic tests. It shows that in April the patient gave a four plus reaction with $\frac{1}{2000}$ c c of serum, in August with $\frac{1}{500}$ c c, in January with $\frac{1}{200}$ c c, in February with $\frac{1}{100}$ c c and that in March $\frac{1}{10}$ c c of serum was required to give a four plus reaction. (I have chosen arbitrarily the set-up of test 3 for serum titrations). In other words, between July and February almost no improvement was shown serologically by the ordinary diagnostic tests (Table 8), whereas titrations disclosed the fact that the patient had only $\frac{1}{1000}$ the amount of complement fixing body in his blood in March as he had at the beginning of treatment. In other

TABLE 10—EXAMPLE OF A SO-CALLED WASSERMANN-FAST CASE. SERUM WAS AT NO TIME INTENSELY POSITIVE. HOWEVER, IT WAS NOT MATERIALLY ALTERED DURING ELEVEN MONTHS BY MANY DIFFERENT PLANS OF TREATMENT. CASE APPEARS CLINICALLY TO BE ONE OF IMPENDING PARESIS.

Serum	March	April	May	Aug	Sept	Dec	Feb
1 10 c c	4+	4+	4+	4+	4+	4+	4+
1 15 c c	4+	4+	4+	4+	4+	4+	4+
1 20 c c	4+	4+	4+	4+	4+	4+	4+
1 30 c c	4+	4+	4+	4+	4+	3+	4+
1 40 c c	4+	4+	4+	4+	4+	2+	4+
1 60 c c	4+	4+	4+	4+	4+	—	4+
1 80 c c	4+	4+	2+	2+	4+	—	2+
1 120 c c	3+	3+	—	—	2+	—	—
1 160 c c	1+	—	—	—	—	—	—
1 240 c c	—	—	—	—	—	—	—

words, instead of being serologically unfavorable, he was actually favorable, considering the fact that he was a late case. In following therapy by means of the Wassermann reaction, the occasional sending of blood to a laboratory or to several laboratories for Wassermann tests may give the poorest possible information concerning the results of therapy and concerning prognosis, unless the physician acquaints himself with the type and delicacy of the method used by his laboratory consultant. Both patient and physician can be unnecessarily discouraged and misled by the continued finding of a four plus reaction obtained by a sensitive method.

Repeated titrations on patients under treatment make the so-called Wassermann-fast case appear much less common. The blood illustrated in Table 9 would appear (falsely) to be Wassermann-fast if the diagnostic tests 1, 2 or 3 alone had been used. In Table 10 is shown what appears to be an example of a real Wassermann-fast case. This patient (with impending paresis) had been under treatment for months before

he came under observation. While under my care he showed practically no improvement, although many different plans of therapy were employed. Repeated tests made over a period of eleven months showed that the blood serum, although at no time intensely positive, was almost as strongly positive at the end as it was at the beginning of treatment (it gave a four plus reaction with $\frac{1}{60}$ c c of serum). In fact, at no time was the Wassermann reaction reduced to the point where less than $\frac{1}{20}$ c c would give a four plus reaction with test 3. Failure to improve serologically is a bad prognostic sign. A patient who persistently, and in spite of treatment, fails to improve serologically, or who improves while under treatment and quickly drops back (in from one to three months) when treatment is discontinued, does not do well eventually, as a rule.

SUMMARY AND CONCLUSIONS

The ideal Wassermann reaction is the result of a test sensitive enough to be positive in every case of active syphilis and negative in patients not afflicted with syphilis. Such a test, however, is a theoretical and practical impossibility. A test sensitive enough to be positive in the great majority of patients with late syphilis is, of necessity, so sensitive that it will be positive in a certain proportion of patients who do not have syphilis. On account of this I have used for several years a five tube test, two tubes of which I have endeavored to make delicate enough to give a positive result almost invariably in patients with active syphilis, two tubes so coarse or insensitive as virtually never to give a false positive, and one intermediate tube.

In this paper I have compared the clinical and serologic findings in a series of chronic medical cases to determine, if possible, the exact value and significance of both positive and negative reactions in each tube (set-up in the five different ways described previously). The most sensitive tube (cholesterinized antigen 0.4 per cent, one unit of complement, icewater bath incubation) was found by titration to be approximately eight times as delicate as the least sensitive one (alcoholic extract antigen, two units of complement, icewater bath incubation).

The tabulations showed that tube 1 (extremely sensitive) gave a four plus reaction in 95 per cent of patients in whom syphilis could be demonstrated by other means, a one to three plus reaction was obtained in four of the remaining 5 per cent of cases, and a flat negative was obtained in less than 1 per cent. It came out four plus in 31 per cent of miscellaneous medical cases regardless of diagnosis. Of this 31 per cent which gave positive tests, syphilis could be demonstrated by other methods in only 32.7 per cent. In other words, 67.8 per cent were apparently false positives. Furthermore, it was found that of patients who gave a positive reaction in this tube with negative reactions with

the coarser ones, apparently 93.5 per cent were false positives. A positive reaction with a test of this delicacy, therefore, is of no value whatever in the positive diagnosis of syphilis. A negative reaction, however, is very useful in its exclusion.

Tube 5, which was relatively insensitive (noncholesterinized antigen with two units of complement and icewater bath incubation) came out positive in 57 per cent of patients who had syphilis which could be demonstrated by other means. Syphilis was proven positively in 98 per cent of patients who gave a four plus reaction in this tube. No evidence of syphilis was found in the remaining 2 per cent. This might have been attributable, however, in part, to the circumstance that they were not examined adequately. A positive reaction with tests of this delicacy (only moderately sensitive) is believed, therefore, to be almost proof positive of syphilis. It is quite apparent, however, that a negative reaction could be of no value whatever in its exclusion.

The intermediate tube 3 (cholesterinized antigen 0.2 per cent with two units of complement and icewater bath incubation) was less interesting and useful than the more extreme ones. It gave four plus reactions in 75 per cent of patients with proven syphilis. It came out four plus in 85 per cent of miscellaneous medical cases (including syphilis). Only 73 per cent of this latter group of positives were false positives. Of the miscellaneous cases, however, which gave positive reactions in this tube with negatives in the less sensitive tubes (4 and 5), 30 per cent were apparently false positives. The dependability of both positive and negative reactions obtained by a test of this delicacy, therefore, would appear to be practically nil.

The above statistics are of additional interest because of the fact that they were obtained almost entirely from a study of chronic late cases of syphilis.

Judging from the data recorded, it seems apparent that if extremely sensitive and reasonably coarse (or insensitive) tests are carried out simultaneously, valuable information can be gained not only concerning the positive diagnosis of syphilis but also concerning its exclusion. This divides medical cases into three classes, so far as the diagnosis of syphilis is concerned, namely, those in whom syphilis can be diagnosed positively by blood examination alone (that is when every test reacts four plus), those in whom the possibility of syphilis can be almost excluded by blood examination alone (that is when every test is negative), and those in which blood examinations are of no service whatever (that is when the sensitive tests react positive and the less delicate ones negative to three plus). In cases of this class the diagnosis or exclusion of syphilis must be based entirely on history, physical examination, lumbar puncture and therapeutic test.

False positive reactions with sensitive tests were obtained more frequently in individuals who were ill than it was in a series of healthy individuals who were tested as candidates to be donors for blood transfusion. It was also observed that false positive reactions of this type were obtained more frequently in patients who had goiter (regardless of size and toxicity) extreme ptosis, active tuberculosis, chronic sepsis, hypertension, pernicious anemia, diabetes and atrophic arthritis, than it was in individuals who did not have these diseases. In no instance, however, did patients with the above diseases in whom the possibility of syphilis could apparently be excluded, give four plus reactions with the less sensitive tests (4 and 5).

In following the results of treatment, simple diagnostic tests in our hands were misleading. The real progress of a patient can be followed much more satisfactorily, so far as serology is concerned, by the use of titrations.

I wish to acknowledge with pleasure the expert assistance in this work of Miss Elizabeth Leas, clinical laboratory assistant.

STUDIES IN ASYMPTOMATIC NEUROSYPHILIS

III THE APPARENT INFLUENCE OF PREGNANCY ON THE INCIDENCE OF NEUROSYPHILIS IN WOMEN *

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In the second paper of this series¹ it was pointed out that in spite of the fact that clinical neurosyphilis is more common in men than in women, cytobiologic abnormalities in the cerebrospinal fluid of primary and secondary syphilitics are equally frequent in the two sexes. Furthermore, evidence was presented to show that from the group of patients showing these early fluid abnormalities (early asymptomatic neurosyphilis) arise most, if not all, of the late cases of clinical meningeal and parenchymatous neurosyphilis. Since women are comparatively exempt from clinical neurosyphilis, there must be some special factor, applying only to the female sex, which inhibits its development. It was suggested that pregnancy might be the factor in question. The purpose of this paper is to examine this point more in detail.

The literature is replete with statistics, dating from the earliest days of the study of syphilis, regarding the comparative incidence of neurosyphilis in the two sexes. The most complete are those recently published by Gartner² on general paresis. He finds, on the basis of the incidence of paresis over a period of years in a population of about 38,000,000 Germans, that the ratio of paretic men to women is 3.43:1. Gartner and other authors, notably Fournier,³ suggest that this difference is largely due to the higher incidence of syphilis in men than in women, together with extraneous factors such as the greater stress of masculine activities.

Virtually, all women with acquired syphilis are within the child bearing period and are thus subject to any influence which pregnancy

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1 Moore, J. E. Studies in Asymptomatic Neurosyphilis. II. The Classification, Treatment, and Prognosis of Early Asymptomatic Neurosyphilis, *Bull. Johns Hopkins Hosp.* 33:231 (July) 1922.

2 Gartner, W. Ueber die Häufigkeit der progressiven Paralyse bei kultivierten und unkultivierten Völkern. Eine statistische, biologische, und Immunitätsuntersuchung über die Syphilis, *Ztschr. f. Hyg. u. Infektionskr.* 92:341 (July) 1921.

3 Fournier, A. Les Affections Parasyphilitiques, Rueff et Cie, Paris, 1894, p. 168 et seq.

may exert Congenital neurosyphilis, however, for example, juvenile paresis, develops in most instances before the child bearing age In this condition, according to statistics gathered by Schmidt-Kraepelin,⁴ both sexes are about equally affected, with only a slight preponderance of males

Statistical data from the Syphilis Clinic of the Johns Hopkins Hospital are available for the examination of this problem The clinic is for charity patients only Its clientele is almost equally divided between the white and colored races As to sex, there are about equal numbers of white and colored males, but colored females predominate over white women in the ratio of about 3 2 This racial distribution must be taken into consideration in connection with the percentage data given for the sex incidence of neurosyphilis The comparative freedom of negroes from neurosyphilis⁵ tends to distort the percentages somewhat in favor of the female sex For the purpose of the present discussion, however, the question of race has been disregarded, since

TABLE 1—THE INCIDENCE ACCORDING TO SEX OF VARIOUS TYPES OF SYPHILIS, AND ESPECIALLY NEUROSYPHILIS, BASED ON THE ADMISSION DIAGNOSIS OF 5,410 SYPHILITIC PATIENT

Diagnosis	Male		Female	
	Number of Cases	Per Cent of Total Males	Number of Cases	Per Cent of Total Females
Early syphilis (primary and secondary)	1,089	36 60	601	21 77
Late syphilis (tertiary)	722	24 29	643	26 37
Neurosyphilis {				
Tabes	110	4 71	22	0 90
General paresis	207	6 96	19	2 01
Meningeal	50	1 68	22	0 90
Vascular	33	1 11	7	0 28
Unclassified	175	5 88	56	2 37
Latent syphilis	715	21 06	1,130	47 57

both whites and blacks are subject alike to the factor of pregnancy The social level of these patients needs little explanation For the most part, they are unskilled laborers and their families

Reference to Table 1 shows that of 5,410 patients with syphilis, 54 per cent are males, 46 per cent females There is, thus, no great preponderance of syphilis in men in this class of patients In order to emphasize the influence of pregnancy on the disease, all admission diagnoses have been tabulated Marked sex variations are apparent in three of the four groups The lower percentage of females with early syphilis is partly due to the anatomic difference in the sexes, with the consequent difficulty of detection of primary syphilis in the female (Secondary syphilis is about equally frequent in the two sexes 22 9

4 Schmidt-Kraepelin, T Ueber die Juvenile Paralyse, Monograph d Gesamtgebiete d Neurol u Psychiat, Julius Springer, Berlin 20 1920

5 Zimmerman, E L A Comparative Study of Syphilis in Whites and Negroes, Arch Dermat & Syph 4 75 (July) 1921

per cent males as against 21.5 per cent females) No sex variation is evident in the incidence of tertiary syphilis Latent syphilis, however, is twice as frequent in women as in men This striking difference is due, together with part of the variation in the incidence of primary syphilis, to the effect of pregnancy on the course of the disease No less than 470, or 42 per cent, of the women with latent syphilis, were pregnant on admission to the clinic

The fact that women who bear syphilitic children often give no history of syphilis and present no signs of the disease (except a positive blood Wassermann reaction) has long been common knowledge A study of the pregnant women in this clinic, now in progress, has convinced us that the usual early manifestations of syphilis are markedly altered by the occurrence of pregnancy A woman infected at or shortly after the time of conception usually does not develop a chancre or secondary syphilis When infection takes place late in pregnancy, on the other hand, the usual course of events may follow, but is often much delayed Substantiation of these clinical data in experimental syphilis is furnished by the recent work of Brown and Pearce⁶

If such striking alterations in the early course of the disease can be caused by a concurrent pregnancy, it is of great interest to examine the later course of syphilitic women who have been pregnant as contrasted with those in whom no pregnancy has occurred since infection In the preceding paper of this series, it was shown that the incidence of spinal fluid abnormalities in 113 women with primary or secondary syphilis (examination of the fluid having been carried out, in most instances, within the first two years of the disease) was 22.1 per cent, as compared with 21.6 per cent in a similar group of 217 men None of these women were pregnant at the time of infection, and all had passed through the usual course of early syphilis This is a satisfactory demonstration that in the early stages of the disease, when pregnancy can be excluded as a modifying factor, the nervous systems of both sexes are equally liable to invasion by the organism In order to determine, therefore, the possible influence of pregnancy, late syphilis only (of more than one year's duration) should be chosen There must be contrasted the incidence of clinical neurosyphilis and of spinal fluid abnormalities, first in women as compared with men, and second in a group of women who were pregnant at or since infection as compared with a group who have had no pregnancies

In Table 1 it is shown that 20.38 per cent of the cases in males were diagnosed as being clinically neurosyphilitic on admission, as

6 Brown, W. H. and Pearce, L. On the Reaction of Pregnant and Lactating Females to Inoculation with *Treponema Pallidum*, A Preliminary Note, *Am J Syph* 4: 593 (Oct.) 1920

compared with only 6.47 per cent of the females. For every case of neurosyphilis in the female, therefore, there are 3.13 cases in the male. Further analysis shows the following ratios:

Cerebrospinal syphilis (unclassified)	for 1 female, there are 2.48 males
Tabes dorsalis	for 1 female, there are 6.36 males
General paresis	for 1 female, there are 4.22 males
Meningeal neurosyphilis	for 1 female, there are 2.27 males
Vascular neurosyphilis	for 1 female, there are 4.71 males

These figures are more accurate than those usually given since they are based on the total number of male and female patients with syphilis, rather than on neurosyphilitics only. With regard to the proportion of pregnant and nonpregnant females, data regarding this series are not available. Junius and Arndt,⁷ however, to mention only one of many articles dealing with this point, state that from 47 to 49 per cent of paretic women are sterile, as compared to 16 or 20 per cent of childless women in the general population. These authors,

TABLE 2—THE INCIDENCE OF SPINAL FLUID ABNORMALITIES IN LATE SYPHILIS WITHOUT EVIDENCE OF NEUROLOGIC DAMAGE. A COMPARISON OF MEN AND WOMEN

Diagnosis	Male			Female		
	Total Cases	Abnormal Fluids	Per Cent Abnormal	Total Cases	Abnormal Fluids	Per Cent Abnormal
II Recurrent	8	2	25.0	4	—	0.0
II Late	2	—	—	1	—	—
III Skin and mucous membrane	30	8	26.6	39	3	7.8
III Bone	40	5	12.5	31	4	12.9
III Cardiovascular	38	7	18.4	10	2	20.0
III Visceral	14	4	28.5	17	—	—
Latent	177	39	22.0	131	29	22.1
Total	309	65	21.03	233	38	16.3

and others, have all dealt with the subject from the standpoint of the influence of syphilis on child bearing, to show that syphilis causes sterility. So far as I am aware, it has not been suggested heretofore that pregnancy may alter the incidence of neurosyphilis in women, and that about half the paretic females may be paretic because of their sterility.

A further important point is the incidence of abnormal spinal fluids in late syphilitics without demonstrable neurologic abnormalities. For examination of this question 542 patients from this clinic are available. It is shown in Table 2 that of 309 men, 21.03 per cent had abnormal fluids, as compared with 16.3 per cent fluid abnormalities in 233 women. The percentage of abnormal spinal fluids in late syphilis of males is almost the same as the percentage in early syphilis (21.03 as

⁷ Junius, P., and Arndt, M. Ueber die Deszendenz der Paralytiker, *Ztschr f d Ges Neurol u Psychiat* **17** 303, 1913.

compared with 22.9) In women, on the contrary, spinal fluid changes are less frequent in late than in early syphilis (16.3 per cent as compared with 22.1 per cent)

If pregnancy is a factor of importance in causing this lowered incidence, those women with late syphilis who have been pregnant since their infection should show a lower proportion of abnormal fluids than those who have never been pregnant That this is actually the case is shown in Table 3 Of ninety late syphilitic women who had never been pregnant, or had borne children only before infection with syphilis, 22.2 per cent had abnormal fluids, while of 142 cases in which pregnancy had occurred one or more times after infection, only 11.2 per cent were thus abnormal The same phenomenon is observed whether tertiary manifestations of syphilis were present, or whether the disease was latent The proportion of spinal fluid abnormalities in late syphilis, when no pregnancies have occurred, is thus precisely the same as that observed in early syphilis In pregnant women, this percentage is reduced by one half

TABLE 3—THE COMPARATIVE INCIDENCE OF LATE ASYMPTOMATIC NEUROSYPHILIS IN WOMEN, SHOWING THE EFFECT OF PREGNANCY ON THE DISEASE

Diagnosis	Syphilis Contracted at Conception or Pregnant Since Infection			Never Pregnant Since Infection		
	Total Cases	Abnormal Fluids	Per Cent Abnormal	Total Cases	Abnormal Fluids	Per Cent Abnormal
Tertiary	54	2	3.7	44	7	15.9
Latent	89	14	15.6	46	13	28.2
Total	143	16	11.2	90	20	22.2

Included in the "pregnant" group are a considerable number of cases of conceptional syphilis—that is, infection with syphilis simultaneously with conception, and with consequent suppression of the early lesions of the disease Thus a history of primary or secondary syphilis was obtained in only 21.8 per cent of the patients in this group, as contrasted with 53.4 per cent in the "never pregnant" group of women, and with 85.5 per cent of males

When infection with syphilis and pregnancy occur simultaneously, there can be no doubt that some factor in connection with the pregnancy inhibits the development of grave syphilitic lesions This being so, one may ask if pregnancies occurring some time after infection confer the same sort of protection, and whether repeated pregnancies protect even more than a single one As regards the former of these points, no information is at present available In Table 4 is shown the percentage of abnormal spinal fluids in women who had had from one to five or more pregnancies since infection There would seem to be

some protective influence exerted by repeated pregnancy, though the statistics are based on too small numbers and are, therefore, too irregular to be of much value. However, the percentage of abnormal fluids in those women who had two or more pregnancies is only 9.3, as compared with 19.5 in primiparae.

TABLE 4—THE INCIDENCE OF LATE ASYMPTOMATIC NEUROSYPHILIS IN WOMEN, GROUPED ACCORDING TO THE NUMBER OF PREGNANCIES SINCE INFECTION

Number of Pregnancies	Total Cases	Abnormal Spinal Fluid	Per Cent Abnormal
0	90	20	22.2
1	41	8	19.5
2	36	3	8.3
3	20	3	15.0
4	21	1	4.7
5 or more	19	2	10.5

It is not suggested that pregnancy occurring some time after infection, the woman having passed through the usual course of early syphilis, may exert any influence on the subsequent development of neurosyphilis. A larger series of cases than the present one is needed for examination of this point. Nor does the silent course of conceptional syphilis protect absolutely against later neurosyphilis. It is a well established clinical fact that in males, a mild early syphilis predisposes to neurosyphilis, possibly because of some alteration in the immune reactions of the body. In women, on the contrary, the factor of pregnancy in some way alters the defense mechanism so that the absence of early syphilitic lesions does not render the nervous system more susceptible to invasion. In this series, for example, spinal fluid abnormalities were present in 20.4 per cent of eighty-three women, who, regardless of pregnancy, gave a definite history of primary or secondary syphilis, while of 161 women in whom such a history could not be obtained, only 13 per cent had abnormal fluids.

CONCLUSIONS

- 1 Clinical neurosyphilis is about three times as frequent in men as in women.
- 2 The nervous systems of the two sexes are, however, invaded with equal frequency in the early stages of syphilis, as is shown by the relative percentages of spinal fluid abnormalities.
- 3 The course of early syphilis is markedly altered by the simultaneous occurrence of pregnancy.
- 4 Pregnancy is the most important point of difference in the ordinary life history of the two sexes.

5 In women with late syphilis (of more than one year's duration), the incidence of abnormal spinal fluids is twice as high in a group of sterile women as in a group in which one or more pregnancies have occurred since infection

6 Almost half of the women who are clinically neurosyphilitic have not been pregnant since infection

7 Multiparae seem to be less liable to late asymptomatic neurosyphilis than primiparae

8 It is suggested on the basis of this study that pregnancy is one factor which may partially account for the comparative freedom of women from neurosyphilis

THE SPECIFIC GRAVITY OF THE URINE *

T ADDIS, M D, AND MARJORIE G FOSTER, M D

SAN FRANCISCO

The experiments reported in this paper were planned to determine whether there might not be certain special conditions under which the specific gravity of the urine could be used as a means for estimating the amount of secreting tissue in the kidney

In 1914 Hedinger and Schlayer¹ described a method in which renal function was studied by observations of the specific gravity, volume, and chlorid content of collections of urine made at short intervals over a period of twenty-four hours. The modification of this test introduced by Mosenthal² has been used widely in this country. The interpretation of the results has given rise to much discussion but it has never been maintained that the test can be taken as a measure of the amount of renal tissue, in fact, Schlayer³ has taken pains to point out that such an interpretation would be quite unwarranted. It would seem, then, that altogether other conditions than those hitherto used would have to be imposed if structural deductions are to be drawn from specific gravity changes in the urine.

Of course, it is evident, no matter what conditions are set, that the specific gravity by itself cannot be used for this purpose. It would have to be combined with a measurement of the volume of urine excreted during a definite period of time. The most that can possibly be learned from the specific gravity alone is the concentration of solids in the urine, and a concentration can never give information about the size of the kidney. This is sufficiently shown by the fact that the small kidneys of a child can produce as concentrated a urine as can be attained by the much larger kidneys of an adult. But if the specific gravity really does give the concentration of solids in the urine it can be used in conjunction with a determination of the rate of urine excretion to measure the amount of solids excreted per unit of time. This is a measurement which might very well be related to the amount of secreting tissue in the kidney.

There are two ways in which the capacity of the kidneys to produce a urine of high specific gravity may be put under strain. Fluids may be restricted, or the amount of solids calling for excretion may be increased. If both conditions were applied simultaneously it might be expected that a maximum effort of the concentrating capacity of the

* From the Department of Medicine of Stanford University Medical School

1 Hedinger and Schlayer. *Deutsch Arch f klin Med* **114** 120, 1914

2 Mosenthal. *Arch Int Med* **16** 733 (Dec) 1915

3 Schlayer. *Beih z med Klin* **9** 211, 1912

kidneys would be required. With this idea the effect of the ingestion of various solids on the specific gravity of the urine of subjects who were abstaining from fluids was observed.

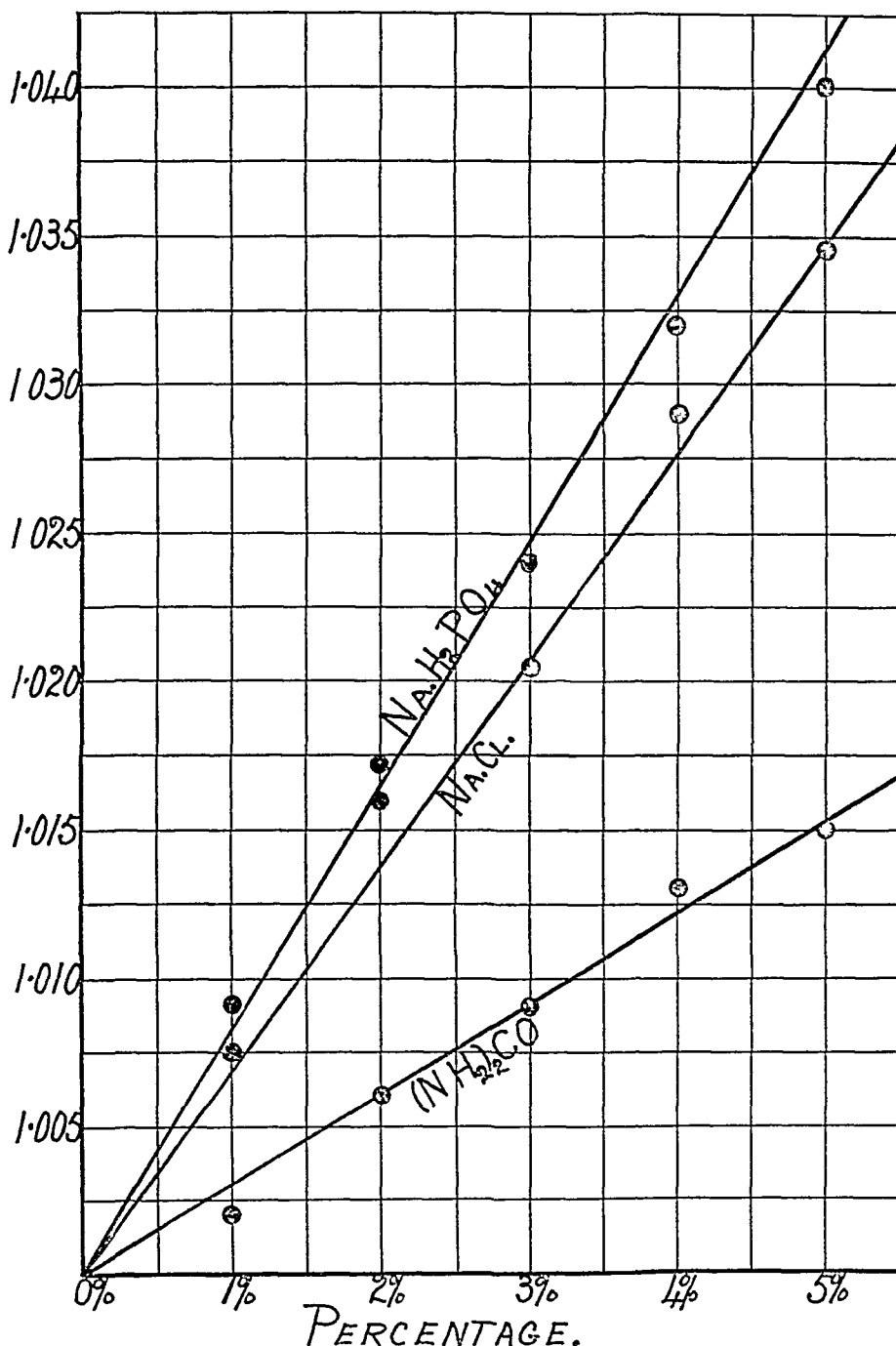
Five experiments were carried through on a group of ten students. In the first experiment the effect of simple fluid restriction was determined. For thirty-six hours no fluids of any kind were taken. The diet was quantitatively and qualitatively constant, and consisted mainly of starch and sugar. The protein and salt content was low, and all substances which might tend to increase the excretion of water through the kidneys were excluded. The collection of urine was started after twenty-four hours' abstention from fluids and covered the twelve hours of the night from 8 p. m. to 8 a. m. In the other experiments the same conditions were observed, except that at 8 p. m. various solids dissolved in 200 c. c. water were taken. In the second experiment, 30 gm. urea were used, in the third, 10 gm. sodium chlorid, in the fourth, 10 gm. sodium acid phosphate, and in the fifth, a mixture of 30 gm. urea, 5 gm. sodium chlorid and 5 gm. sodium acid phosphate was taken. The average specific gravities and volumes of the twelve hour night urines are given in the accompanying table.

AVERAGES FROM TEN NORMAL PERSONS UNDER FIVE DIFFERENT CONDITIONS

Conditions	Sp. G.	Volume in C. c.
Fluid restriction only	1.027	242
Fluid restriction and addition of 30 gm. urea in 15 per cent concentration	1.025	597
Fluid restriction and addition of 10 gm. sodium chlorid in 5 per cent concentration	1.028	391
Fluid restriction and addition of 10 gm. sodium acid phosphate in 5 per cent concentration	1.035	213
Fluid restriction and addition of 30 gm. urea, 5 gm. sodium chlorid and 5 gm. sodium acid phosphate given in 200 c. c. water	1.025	616

Contrary to expectation, these figures show that the specific gravity of the urine is not greater after the addition of urea, sodium chlorid or a mixture of urea, chlorid and phosphate, than after fluid restriction alone. This is partially explained by the increase in urine volume which followed the administration of these substances, just as the relatively high specific gravity after sodium acid phosphate can, in part, be explained by the associated reduction in the volume of the urine. But the main point of interest lies in the fact that the specific gravity results cannot be accounted for fully by the urine volume changes. Their inadequacy can be shown by a consideration of the amounts of urea, chlorid and phosphate which were excreted. Thus, in the experiment with simple fluid restriction the total amount of all three substances was 8.44 gm. ($(\text{NH}_2)_2\text{CO}$, 5.40 gm., + NaCl, 1.78 gm., + NaH_2PO_4 , 1.26 gm.). When the mixture was taken the total amount eliminated was 30.19 gm. ($(\text{NH}_2)_2\text{CO}$, 22.00 gm., + NaCl, 4.63 gm.

+ NaH_2PO_4 , 3.56 gm) It would be conservative to assume that these three substances together made up more than 75 per cent of the total solids of the urine, and the remainder cannot have been far from constant since the urines were from the same group of subjects on a fixed diet. The figures 8.44 and 30.19 may be used as an indication of the



The specific gravity of varying concentrations of urea, sodium chlorid and sodium acid phosphate. The figure shows the wide differences between the specific gravities of equal concentrations of these substances. Thus 3 per cent concentrations of urea, sodium chlorid and sodium acid phosphate have specific gravities of approximately 1.009, 1.020 and 1.024.

relative concentration of total solids in the two experiments. In the one case there is 8.44 gm. in 242 c c., a 3.48 per cent concentration of solids. In the other, there is 30.19 gm. in 616 c c., a 4.90 per cent concentration of solids. If the specific gravity of the urine depended only on the relation between the solids and the water in the urine, we should expect to find a higher specific gravity in a urine with 4.90 per cent solids than in one with 3.48 per cent solids. But the table shows that the reverse is true, for with 3.48 per cent solids the specific gravity is 1.027 and with 4.93 per cent the specific gravity is 1.025.

The explanation of this apparent paradox lies in the fact—known ever since the first specific gravity was measured—that each dissolved substance has its own specific effect on the specific gravity of a solution. This fundamental fact is generally ignored in discussions on the specific gravity of the urine, and, either tacitly or openly, it is assumed that the specific gravity measures the total concentration of solids.

Some rough determinations of the specific gravity of varying concentrations of urea, sodium chloride and sodium acid phosphate are given in the accompanying figure.

This graph shows how it came about that the specific gravity of the urine was lower after taking a mixture of urea, chloride and phosphate, than after simple water restriction, even though the total concentration of solids was greater. It was lower because a greater proportion of the total solids consisted of urea which has less effect in raising the specific gravity than chlorides or phosphates.

The specific gravity of the urine is the resultant of the various effects of all urinary constituents. Since each has its own specific effect and the relative concentrations are unknown, it follows that it is impossible to attach any precise quantitative significance to the results of any method of estimating the total solids of the urine in which specific gravity measurements are used.

CONCLUSIONS

The specific gravity of the urine of normal persons was measured under varying conditions designed to place a strain on the concentrating activity of the kidney. It was found that not even an approximate idea of the work of the kidney in the excretion of solids could be obtained from the results. It is therefore concluded that specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney.

A TEST OF THE CAPACITY OF THE KIDNEY TO PRODUCE A URINE OF HIGH SPECIFIC GRAVITY¹

T ADDIS, M.D., AND MARIAN C SHEVKY
SAN FRANCISCO

Although it has been shown in the preceding paper that the specific gravity of the urine cannot be used as a means to determine the rate of excretion of solids, and although it must be regarded as a very inaccurate method of estimating even that partial function of the kidney by virtue of which it is able to separate a concentrated solution from a blood in which the urinary constituents are relatively dilute, it, nevertheless, remains true that in certain cases specific gravity determinations may give information of considerable clinical value. There is a relation between the inability to produce a urine of high specific gravity and certain extreme grades of renal decompensation. It is this inability which, in certain cases, leads to the constantly low specific gravity in short time urine collections, which is in sharp contrast with the very variable specific gravity of the urine in normal persons. So many examples of this "fixation of specific gravity" at a low level have been given by Hedinger and Schlayer,¹ by Mosenthal,² and by Christian,³ that it may be taken as a well established fact. And, on the other hand, so many far advanced cases of chronic Bright's disease are free or practically free from symptoms, that the demonstration of this inability may be the only indication of the real gravity of the situation in circumstances where only the simplest possible functional tests can be used.

But in this particular functional manifestation, as in all others, the clearest possible separation of normal from abnormal is only to be attained by making use of the principle of strain. This has not been done in the one day renal test of Hedinger and Schlayer, nor in Mosenthal's or Christian's modifications. For this reason, as well as for another given in a later paper, we have determined the variability of the specific gravity in normal persons under conditions specially designed to induce the production of a urine of high specific gravity.

In order that the test might be almost universally applicable, the conditions were made as simple as possible. The subject is instructed to abstain from fluids of all sorts after breakfast on one day until he rises from bed on the morning of the following day, and is told to

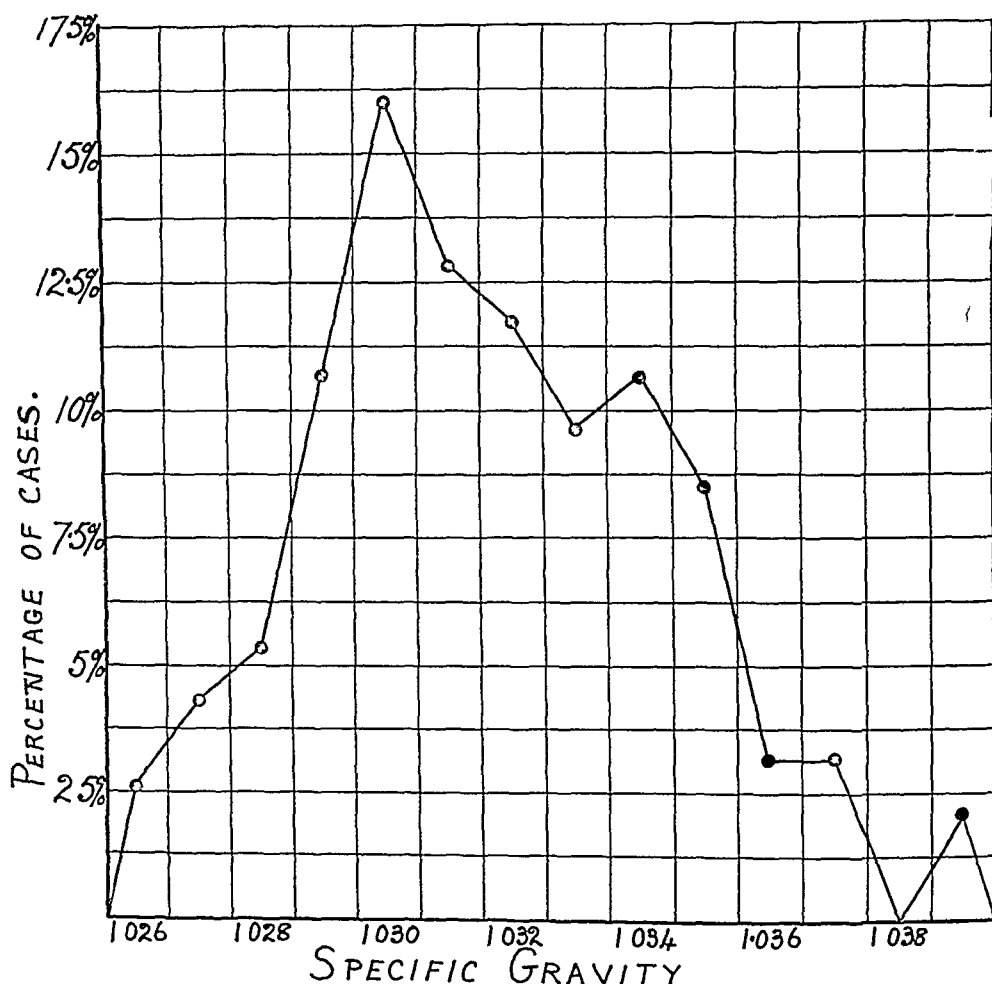
* From the Department of Medicine of Stanford University Medical School

1 Hedinger and Schlayer. *Deutsch Arch f klin Med* **114** 120, 1914

2 Mosenthal. *Arch Int Med* **16** 733 (Dec) 1915

3 Christian. *Oxford Med* **3** 585, 1921

collect a twelve hours' night urine In clinical work in the outpatient department we have found it necessary to give these directions in writing and to provide a wide necked bottle into which the urine is to be voided directly It must be made plain that the urine passed at the beginning of the period of urine collection is to be discarded The whole twelve hours' urine should be collected at one voiding but if this is not possible the patient should be told not to pass urine for at



Percentage frequency distribution of specific gravity of the night urine in normal individuals after restriction of fluids

least three hours before the completion of the specimen The usual diet must be taken except that water, tea, coffee, milk, soup or any other fluid must be avoided When these instructions are given fully, as well as clearly, it seems that few patients make mistakes

We have made ninety-four observations on seventy-five normal persons, most of them medical students The average is 1032, the standard deviation ± 00281 and the variability 88 per cent In the accompanying chart the percentage frequency distribution is given, and

in Table 1 the odds that any normal individual would have as low or a lower specific gravity than certain specified levels are tabulated

TABLE 1—THE ODDS THAT ANY NORMAL INDIVIDUAL UNDER THE CONDITIONS OF THE TEST WOULD GIVE AS LOW OR A LOWER SPECIFIC GRAVITY THAN THOSE GIVEN BELOW

Specific Gravity	Odds
1 026	1 normal in 47
1 025	1 normal in 115
1 024	1 normal in 323
1 023	1 normal in 1,000
1 022	1 normal in 5,000

In these specific gravities from normal persons variations in the amount and the kind of food taken no doubt led to a somewhat greater variability than would otherwise have been found. But in patients a still greater variation in diet may be likely to occur, perhaps enough in some cases to make our normal figures inapplicable as a standard of comparison. The specific gravities of a few normals under the usual conditions and after taking from 1 to 1.5 pounds of steak with their evening meal were compared. Table 2 shows that there was no appreciable difference.

TABLE 2—COMPARISON OF SPECIFIC GRAVITIES IN NORMALS WITH USUAL DIET AND WITH HEAVY MEAT DIET

Name	Usual Diet	Usual Diet + 1 Pound or More of Steak at 6:30 P. M.
B	1 032	1 029
T	1 027	1 026
L	1 030	1 033
C	1 028	1 029
N	1 035	1 032
H	1 035	1 030
Average	1 032	1 030

Some of our patients had been on a low salt and low protein diet before the test was used, and in normal persons this type of diet seems to make the specific gravity lower and more variable. Table 3 shows a comparison between specific gravities under the ordinary unrestricted dietary conditions and those obtained after the subjects had lived for forty-eight hours on food with a very low salt and a low protein content.

A specific gravity somewhat lower than normal obtained from a patient whose salt and protein intake has been restricted might then be due entirely to the diet. But even when the diet is unrestricted, low specific gravities in patients must always be interpreted with caution. There is the ever present possibility that the patient has not abstained

from fluids or has failed to discard the urine passed at the commencement of the twelve hour period. And, then, of course, there are many extrarenal factors in patients which may lead to an unusually large excretion of water and so to a low specific gravity, even though the

TABLE 3 — COMPARISON OF SPECIFIC GRAVITIES IN NORMALS ON ORDINARY UNRESTRICTED DIETARY AND ON VERY LOW SALT AND LOW PROTEIN DIETS

	Name	Usual Diet	Low Salt and Protein Diet
N		1 035	1 020
W		1 030	1 033
H		1 035	1 029
L		1 030	1 031
Wa		1 032	1 027
T		1 027	1 019
Average		1 032	1 027

concentrating capacity of the kidneys is unimpaired. On the other hand, there is never any doubt about the meaning of a high specific gravity, and it is here that the test has its main clinical value. For when a specific gravity within the normal range has been achieved a positive fact has been established which in itself is probably sufficient to exclude the possibility of the existence of that terminal stage of renal decompensation which so often develops insidiously in cases of chronic Bright's disease.

The specific gravities found in various types of renal lesion will be discussed and compared with other functional results in a later paper.

CONCLUSION

A simple test of the capacity of the kidney to produce a urine of high specific gravity is described. In normal individuals, after restriction of fluids, the average specific gravity is 1 032 with a standard deviation of ± 00281 . These figures may be used as a normal standard for comparison with observations made on patients under the same conditions.

STUDIES ON BLOOD LIPOIDS

I THE RELATION OF CHOLESTEROL AND PROTEIN DEFICIENCY TO BASAL METABOLISM *

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Cholesterol possesses many points in common with the fats and lipoids and is, therefore, usually grouped with these substances. Its presence in the blood seems to go hand in hand with that of the fats, and the quantitative relationship it bears to them is fairly constant. By virtue of this and the fact that it can readily be determined quantitatively, estimates of cholesterol are often used as a measure or index of the total fat content of the blood. The origin of the cholesterol of the blood is not definitely known, some of it is undoubtedly exogenous, and some endogenous. It is subject to marked fluctuations under a variety of conditions. In some it appears to be independent of external causes and definitely associated with metabolic disturbances, as in diabetes, nephritis,¹ etc. There also can be no doubt of the relation of the blood cholesterol to the glands of internal secretion, particularly the suprarenal (Rothschild et al) and the thyroid (Luden²). The question arises whether the lipid variations in disturbances of metabolism and internal secretion are incidental, or if a definite relationship between them can be established.

With these facts in mind, studies have been undertaken for the purpose of correlating basal metabolism and blood cholesterol findings in a group of cases in which both are subject to fluctuation. Thus, the study embraces cases of exophthalmic goiter, thyroid adenoma, nephritis and nephrosis, myxedema, menopause and related conditions. In addition, certain other conditions in which one or the other factor (basal metabolism or cholesterol) is disturbed, have been studied for purposes of comparison.

The cholesterol determinations have been made by the Bloor modification of the Funk-Autenrieth method. Because of the nature of this method, the personal equation constitutes an important factor. The majority of the determinations in our cases have been made by Dr Joseph Reiss of our laboratory, who has analyzed more than twelve thousand specimens of blood, a sufficient experience to assure

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* Read before the Section on Medicine New York Academy of Medicine, Nov 17, 1921

1 Epstein A A J A M A **64** 444 (Aug 11) 1917

2 Luden G Collected Papers Mayo Clinic **10** 429, 1918

reliability and to warrant the conclusions which we shall draw from the results obtained. A survey of the figures of a very large series of examinations shows that the normal value for cholesterol in the blood ranges between 160 and 200 mg per 100 c c. By far the largest number show values nearer the upper limit.

The basal metabolism determinations have been made with the original Benedict portable apparatus. Oxygen consumption alone has been measured, a respiratory quotient of 0.82 having been assumed. Surface area has been estimated by the Du Bois-Du Bois height-weight formula. In those cases associated with edema, the weight used in calculation of the surface area was that which preceded the development of the edema, or followed its elimination. In this way, we believe, that the factor of tissue dilution has been eliminated from the estimations.

TABLE 1—EXOPTHALMIC GOITER

Acc No	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Remarks
					Calories	Per Cent		
203475	K C	53	♀	Oct 9	43.4	+20	0.230	Postoperative
				Nov 11	53	+46	0.130	
				Dec 2	55	+54	0.150	
208738	S M	26		Mar 26	43	+14	0.196	
205137	D R	48	♀	Oct 22	67.5	+82	0.090	
				Nov 3	65	+78	0.080	
				Nov 22	58.6	+62	0.140	
				Dec 4	62	+72	0.095	
210167	M M	50	♂	Dec 2	48	+28	0.136	
				Feb 1	44	+15	0.182	
208597	A A	16	♂	Mar 15	62	+37	0.148	Gravid 3 months Chronic nephritis
				Mar 26	54.5	+25	0.178	
207946	M F	40	♀	Mar 5	57	+46	0.166	
208189	N J	41		Mar 1	59	+63	0.130	
209330	I B	38		April 15	61.5	+54	0.124	
209388	I J	23		April 16	51.5	+30	0.106	
210372	M H	28		May 23	52	+40	0.130	
210306	B H	30		May 23	44.8	+20	0.136	
210814	I K	45	♂	June 11	66	+73	0.146	
				June 22	63.5	+65	0.130	
				June 25			0.156	
				Jan 11			0.218	
211111	A C	40	♂	Jan 12	49.5	+25	0.150	
212071	M L	28	♂	Sept 1	48.5	+20	0.114	

Hyperthyroidism (Exophthalmic Goiter)—It will be seen that in all these cases (Table 1) the basal metabolism is increased, and the blood cholesterol figures are below normal. In general the decrease in the blood lipid bears a direct relationship to the extent of increase of basal metabolism. In nine of the fourteen cases this holds true, the lowest metabolic figure, +14 per cent, corresponding to a blood cholesterol of 0.196 per cent, and the highest figure, +82 per cent, corresponding to a cholesterol of 0.090 per cent. This relation is not invariable, however. In three cases (I J, B H, and M L) the cholesterol figure is low in proportion to the increase of basal metabolism. These three cases are of two years' duration and it is not unfair

to assume an exhaustion of lipid, which outlasted the elevation of the basal metabolism. The rising cholesterol figures in the case of I J are explained by a complicating nephritis. In the case of M F the cholesterol is higher than would be anticipated in a toxic case with a rate of +46 per cent, and this discrepancy is not easily explained. Cases in which more than one determination has been made, however, show clearly that an inverse relationship exists between the metabolic rate and the cholesterol content of the blood, as was also found by Luden in a case of myxedema treated with thyroxin.²

TABLE 2—NONTOKIC THYROID ENLARGEMENTS (ADENOMAS)

Acc No	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Remarks
					Calories	Per Cent		
205905	A G	27	♂	Nov 27	40	+ 6	0 162	
206087	L R	58	♂	Dec 2	44	+15	0 162	
207838	J B	60	♂	Dec 23	42 5	+12	0 184	
208589	A K	46	♂	Jan 4	33 3	— 7	0 178	
	O O	27	♂	Jan 4	33 3	— 8	0 180	
210912	F F	53	♀	May 17	38 5	+ 5	0 188	

In Table 2, six cases of thyroid enlargement without clinical signs of toxicity are tabulated. The blood cholesterol figures range from 0 162 to 0 188 per cent, the basal metabolism from —8 to +15 per cent, variations which may be regarded as ranging fairly within the normal.

TABLE 3—TOXIC THYROID ENLARGEMENT (ADENOMAS)

Acc No	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Remarks
					Calories	Per Cent		
204896	A S	40	♀	Oct 19	40	+ 9	0 328	
				Nov 1	42	+15	0 218	
				Nov 20	45	+24	0 238	
				Dec 9	36 8	Normal	0 278	
204922	E J	45	♂	Oct 17	50 2	+38	0 178	Partial thyroidectomy November 29
205312	M S	51	♀	Nov 1	49 8	+38	0 120	Auricular fibrillation
206947	A P	38	♂	Dec 16	47 3	+20	0 148	
208768	A R	46	♂	Mar 26	49	+36	0 164	
209002	M H	46	♂	April 2	46	+18	0 130	
209661	C T	61	♂	April 29	56	+58	0 174	Moderate dyspnea
209878	S M	49	♂	May 12	53	+48	0 130	
212972	H H	48	♂	Sept 1	53 3	+38	0 132	
213154	M K	49	♀	Sept 8	52	+44	0 160	

In Table 3 the findings are recorded in ten cases of thyroid enlargement (adenomas) showing toxic signs clinically and an increase of basal metabolism. In only six of these does the inverse relationship as set forth above, between blood cholesterol and basal metabolism, hold true. In this group also, the cases in which the cholesterol factor is low and out of proportion to the metabolic rate, are of longer duration. There remain four cases in which the blood cholesterol is normal or only slightly diminished, in spite of an increased basal metabolic rate. It

will be noted that these four patients were women at the ages of 45, 46, 49 and 61, respectively, three of the four were at the climacteric period. A series of cases in the menopause will be presented later, which will show that women at this age are subject to a hypercholesterinemia. We may then assume that the inverse relationship still holds true, but in the group of thyroid enlargements, due to sex incidence and the age at which the toxic symptoms developed, the initial figure is higher. Fortunately, we were able to study a case (A S) of definite thyroid adenoma in which toxic symptoms developed while the patient was under observation. The basal metabolism gradually rose from +9 to +24 per cent with a corresponding fall of blood cholesterol of from 0.328 to 0.238 per cent. At this stage a thyroidectomy was performed. Ten days later, the basal metabolism had fallen to normal and the cholesterol had risen to 0.276 per cent.

TABLE 4—CLINICAL DIAGNOSIS (?) HYPERTHYROIDISM (?)

Acc No	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Diagnosis
					Calories	Per Cent		
206107	B S	71	♀	Dec 7	34	-3	0.353	Auricular fibrillation
206274	B R	35	♀	Dec 11	36.6	Normal	0.100	Gastric neurosis
209318	A F	40	♀	Dec 14	32.6	-10	0.218	Paroxysmal tachycardia
207886	R B	17	♀	Feb 16	50	+15	0.170	(?) Hyperthyroidism
208144	L L	24	♀	Feb 26	35.4	-5	0.218	Neurasthenia
219072	M G	42	♀	April 19	39.8	+8	0.296	Neurosis
210822	E W	9	♀	June 14	65	+14	0.218	Exophthalmos
211139	H B	26	♀	June 27	40.5	+2	0.314	Neurosis
211881	M M	56	♀	June 30	38	Normal	0.164	Gastric neurosis
213132	N H	40	♀	Sept 8	40	Normal	0.276	
	M L	34	♀	Dec 4	41	+8	0.189	Visceroptosis

The next group of cases (Table 4) comprises those in which a condition of hyperthyroidism was suspected clinically. These are, for the most part, functional disorders. In this group, the basal metabolism ranges from -10 to +15 per cent. Of these cases, the blood cholesterol is normal in six. In four cases there is an increase in the blood lipid, the cause of which is not clear. In only one case (B R) is the cholesterol below normal. This case is one of gastric neurosis of several months' duration, in which all food was vomited immediately after eating. The patient was undernourished and in a debilitated state and it is in these factors that we must seek the explanation for the low lipid content. This group stands in marked contrast to the true cases of hyperthyroidism with elevated basal metabolism (Table 1) all of which showed cholesterol values below normal. This does not yet establish the value of a low blood cholesterol as a positive aid in the diagnosis of thyroid disease, but, in the absence of other known factors that tend to produce a hypercholesterinemia (diabetes, menopause, pregnancy, nephritis and obesity), a blood cholesterol of normal or

increased value is strong evidence against the existence of a thyrotoxic state. It appears, however, that if repeated examination of the blood indicates a progressive decline of the cholesterol content in the absence of food insufficiency, Addison's disease, or uremia, the fact may be taken as presumptive evidence of the existence of a thyrotoxic condition. This is true even if the cholesterol value of the initial examination of the blood is above normal (Case A S, Table 3)

TABLE 5—CASES WITH SUBNORMAL BASAL METABOLISM AND NEPHRITIS

Acc No	Name	Age	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Diagnostic Notes
				Calories	Per Cent		
204853	Anna L	14	Dec 8	30.7	—18	0.904	Nephrosis
206071	Rose B	27	Dec, 21	32	—15	0.364	Nephrosis Wass 4+
			Jan 6	37.8	Normal	0.552	Had been on thyroid therapy
			Feb 9	34.9	—6	0.460	Antisyphilitic treatment
211792	Fsther S	33	Sept 15	30	—18	0.370	Nephrosis
			Sept 27	30	—18		
			Oct 18	32.8	—10		
207030	Yetta H	44	Oct 29	34.7	—4	0.296	
			Jan 11	29.1	—19	1.350	Myxedema
			Feb 8			0.725	On thyroid therapy
			Feb 15	38.6	+6	0.206	On thyroid therapy
			Mar 31	40	+10		On thyroid therapy
216441	Maud E	29	May 12	29	—19	0.680	Stopped thyro'd after leaving hospital
			Jan 6	34.5	—8	0.508	Nephrosis
			Feb 11	32.6	—13	0.800	
217115	Ira S	35	Feb 8	33.4	—15	0.320	Nephrosis
207745	Yetta R	28	Feb 21	37.6	Normal	0.394	Chronic diffuse nephritis
200949	Peppie W	54	Jan 10	37.4	+6	0.412	Chronic diffuse nephritis
215385	Isidor T	48	Dec 7	41	+6	0.254	Hypertensive nephritis
216350	Hymen B	39	Jan 15	41	+6	0.140	Chronic nephritis
209679	Celia R	32	April 24	33	—11	0.313	Myxedema
212870	Arthur S	20	Dec 1	22.7	—42	0.102	In mition
206706	Rose Y	21	Dec 21	32	—15	0.130	Creatinism
			Dec 30	44.2	+12	0.484	Nephrosis pulmonary tuberculosis

Cases with a Subnormal Basal Metabolism (Table 5) —For many years it has been known that a low rate of metabolism exists in cases of hypothyroidism. More recently conditions of subnormal oxidation have been recognized, the relation of which to the thyroid gland is not clear. A group of unclassified cases with low basal metabolic rates has been reported from the Mayo Clinic. Aub and DuBois, in 1917,³ reported a reduction in metabolism in cases of nephritis with edema and make the following statement: "The reduction of metabolism per square meter of body surface found in nephritic edema is sometimes very marked (from 27 to 40 per cent) and points to some cause other than mere dilution of tissue or skin distention." One of us⁴ has pointed out the possibility of a certain group of chronic nephroses being a metabolic disorder allied to a state of hypothyroidism. The existence

³ Aub, J. C., and DuBois, E. *Arch. Int. Med.* **19**: 865 (May) 1917.

⁴ Epstein, A. A. *J. A. M. A.* **64**: 444 (Aug. 11) 1917, *M. Clinics N. America* **4**: 145 (July) 1920.

of a hypercholesterinemia of unusual degree in both nephrosis and myxedema was noted Eppinger,⁵ Volhard,⁶ and more recently Behr and Waldrop⁷ have reported the beneficial results of thyroid therapy in cases of edema of obscure origin The relationship existing between these cases of nephrosis and the thyroid was demonstrated in a striking manner by the following case

REPORT OF CASE OF NEPHROSIS DEVELOPING MYXEDEMA

History—Yetta H, aged 44, first entered the hospital Sept 25, 1916 Past history is of no importance, except that menopause developed at the age of 28 For four months prior to admission there had been gradually increasing edema with pain in the lumbar region, weakness and anorexia

Physical Examination—Marked generalized edema and pallor

Admission Diagnosis—Chronic nephritis

Urine—The urine contained heavy traces of albumin, hyaline and granular casts and a moderate number of white blood cells No red blood cells

Blood Chemistry—Urea nitrogen, 21 mg per hundred cc, incoagulable nitrogen, 56 mg per hundred cc, cholesterol, 0.400 per cent No basal metabolism studies were being made at Mt Sinai Hospital at this time Blood pressure, 105/80, phenolsulphonephthalein excretion, 48 per cent in two hours Blood Wassermann, negative

Clinical Course—For two weeks the patient was kept on a Karrell diet and then on a salt free diet There was no subsidence of edema or increase of urinary output October 11 she was put on a high protein diet Within a week there was marked diuresis which continued until the edema had entirely disappeared, within three weeks of institution of treatment She was discharged as a case of nephrosis relieved by high protein feeding The albuminuria persisted

Second Admission—Jan 15, 1921, four years and three months later, the patient entered the hospital for the second time During the preceding year there had been increasing weakness, mental dulness, swelling of the face and lids and nocturia On physical examination the patient presented the classical picture of myxedema The skin was harsh, dry and scaly, the hair brittle and sparse The speech was slow and mentality was dull There was marked swelling of the face and lids, nonpitting edema of the extremities and the typical subcutaneous infiltrations of myxedema

Urine Albumin, heavy trace with many hyaline and granular casts

Blood Chemistry—Urea nitrogen, 18.2 mg per hundred cc, incoagulable nitrogen, 37.6 mg per hundred cc, uric acid, 2.3 mg per hundred cc, creatinin, 1.9 mg per hundred cc, cholesterol, 1.350 per cent

Basal Metabolism 29.1 calories—19 per cent The phenolsulphonephthalein output was 45 per cent in two hours

On the basis of these findings, the patient was put on thyroid extract Marked improvement of all symptoms followed, the basal metabolism returned to normal, the blood cholesterol diminished and the loss of 23 pounds in weight in four weeks was noted The effect of thyroid on the metabolic rate and the blood cholesterol is shown in Table 5, the inverse ratio again holding true

⁵ Eppinger, H Zur Pathologie und Therapie des menschlichen Oedems, Berlin 1917

⁶ Volhard Die Doppelseitigen Haematogenen Nierenerkrankungen, Berlin, 1918

⁷ Behr, O, and Waldrop, C P Semana med 28 661 (June 9) 1921

Summary—A case presumably one of nephrosis, on first admission to the hospital responded to a high protein diet with the disappearance of the edema after failure of restricted diets. She returned four years later as a typical myxedema and is relieved of all symptoms by thyroid therapy.

The late development of myxedema in this case of nephrosis may be regarded by some as a coincidence. To us, myxedema represents the extreme stage of a defective metabolism which is similar in character to that occurring in nephrosis. The therapeutic results obtained in certain nephritides with the high protein diet (with and without the addition of thyroid), warrant the conclusion previously reached, that there are borderline cases, on one side of which are those with a clinical picture of nephrosis, and on the other side, the cases of myxedema. For reasons previously pointed out by one of us⁴ nephrosis may be regarded primarily as a condition of defective protein metabolism, characterized chemically by hypercholesterinemia and reduced protein content of the blood serum.

REPORT ON BASAL METABOLISM STUDIES

Basal metabolism studies have therefore been made on ten cases of nephritis and nephrosis (Table 5)

CASE 1—History—Anna L., aged 14, had been subject to frequent attacks of tonsillitis. Tonsillectomy one year ago. Scarlet fever six years ago, so far as can be determined there was no complicating renal condition at the time. For the six months prior to entrance to the hospital there had been gradually increasing edema, dyspnea, frequency and nocturia.

Examination—On admission the physical examination was noteworthy only for generalized edema. The urine contained large amounts of albumin, hyaline and granular casts. Blood pressure, 125/70, phenolsulphonephthalein output was 30 per cent in two hours.

Blood Chemistry—Urea nitrogen, 19.6 mg per hundred c.c., incoagulable nitrogen, 40.3 mg per hundred c.c., uric acid, 2.8 mg per hundred c.c., creatinin, 1.8 mg per hundred c.c., cholesterol, 0.904 per cent. Basal metabolism 30.7 calories (—18 per cent).

Diagnosis—On entrance a diagnosis of chronic diffuse nephritis was made.

Treatment—The patient was put first on a Karrell diet, then on a carbohydrate and high protein diet successively, but apparently with little benefit. A salt free diet and diuretics (theobromin sodio-salicylate) reduced the edema somewhat, and the weight fell from 106 to 97 pounds, but no further removal of fluid could be effected, and conditions remained stationary. Two months after entrance a high protein diet was again instituted, and, in addition, small doses of thyroid extract were given. Within two weeks the edema had disappeared entirely and the weight had dropped to 85 pounds. The failure of the high protein diet at first was due to the fact that it was impossible to get the patient to eat because of her extreme illness. Albuminuria was present at the time of discharge.

CASE 2—History—Rose B., aged 27, whose past history is of no importance, had noticed for eighteen months an increasing swelling of the legs, thighs and external genitalia, pallor and nocturia.

Examination—Pallor and generalized edema. Blood pressure 110/70, phenolsulphonephthalein output was 45 per cent in two hours. The urine contained large amounts of albumin, many hyaline and granular casts, but no

blood cells The Wassermann was four plus A Wassermann test made at the Beth Israel Hospital one year ago was negative

Blood Chemistry—Urea nitrogen, 22.4 mg per hundred cc, incoagulable nitrogen, 47.8 mg per hundred cc, uric acid, 2.4 mg per hundred cc, creatinin, 1.6 mg per hundred cc, cholesterol, 0.364 per cent Basal metabolism 32 calories (—15 per cent)

Treatment—The patient was put on a high protein diet and thyroid extract Within one week after institution of this therapy she began to void large amounts of urine and continued to do so for two weeks At the end of this time the edema disappeared, the weight had dropped from 137 to 122 pounds, and the basal metabolism had risen to the normal value of 37.8 calories Ten days after the disappearance of the edema neo-arsphenamin therapy was instituted, on the supposition that syphilis entered as an etiologic factor, but after four injections, at weekly intervals, it had to be discontinued because of increasing albuminuria This patient was followed in the outpatient department for several months and recurring edema was readily controlled by thyroid

This case is very similar to the one reported by Waldrop and Behl,⁷ as a syphilitic nephrosis with generalized edema, anemia, and high blood lipoids developing in the secondary stage of syphilis, which proved refractory to antisiphilitic treatment, but responded to thyroid therapy with complete disappearance of the edema

CASE 3—History—Esther S., aged 33, was admitted to the hospital, July 15 1921 She had had pyelitis four and a half years previously, salpingitis one year ago For months previous to admission there had been gradually increasing edema, ascites and hydrothorax

Examination—The urine contained three plus albumin, hyaline and granular casts Blood pressure 95/60, phenolsulphonaphthalein excretion, 35 per cent in two hours

Blood Chemistry—Urea nitrogen, 14 mg per hundred cc, nonprotein nitrogen 31.5 mg per hundred cc, uric acid, 4.5 mg per hundred cc, creatinin, 1.5 mg per hundred cc, cholesterol, 0.375 per cent

Treatment—For the first two weeks the patient was put on a high protein diet but with no improvement, with rather a slight increase in edema, the weight rising from 153 to 157 pounds She then was given a salt free low protein diet, with fluids limited to 500 cc and various diuretics (cafein, digitalis and theobromin sodio-salicylate) Her condition grew steadily worse, the edema increased rapidly and September 5 her weight was 175 pounds During this period there was a fluid retention of from 150 to 400 cc daily September 5, the high protein feeding was again instituted, at first with little improvement September 14 examination showed a basal metabolism of 30 calories, a decrease of 18 per cent below normal Thyroid extract was then given Within a week there was a diuresis and for the first time the fluid output exceeded the intake by from 350 to 500 cc daily October 29, the patient weighed 142 pounds the basal metabolism had risen to —4 per cent and only a trace of albumin was being excreted in the urine

CASE 4—History—Maude E., aged 29, had had a bilateral ovariectomy done ten years previously Her present illness began about four months ago with swelling of the legs, arms and face

Examination—Generalized edema of moderate degree Blood pressure 110/70 The urine contained four plus albumin, hyaline and granular casts, the specific gravity was between 1.010 and 1.022, phenolsulphonaphthalein, 30 per cent in two hours

Blood Chemistry—January 6 Urea nitrogen, 182 mg per hundred c c , incoagulable nitrogen, 39.5 mg per hundred c c , uric acid, 2.5 mg per hundred c c , creatinin, 11 mg per hundred c c , cholesterol, 0.508 per cent Basal metabolism 34.5 calories (—8 per cent)

Treatment—A high protein diet and thyroid therapy was followed by the complete disappearance of edema within two weeks. At the same time there was a progressive diminution in the amount of albumin lost in the urine. Then, for some unknown reason, the intense albuminuria recurred, edematous swellings reappeared, the basal metabolism dropped to —13 per cent, and the blood cholesterol rose to 0.8 per cent.

It is evident from this relapse that the cause operative in this case had not been eliminated and that the therapy was inadequate. Increase in the dosage of thyroid resulted in amelioration of the condition, but the ultimate outcome is still in doubt.

CASE 5—History—Ira S., aged 35, had marked generalized edema twelve years previously, accompanied by diminished urinary output. Condition lasted one and a half years. He had a similar attack six years ago and again one year ago. One week before entrance he developed slight generalized edema which cleared up very quickly. He eats freely during these attacks.

Examination—Negative, no cardiac hypertrophy or edema. Blood pressure 105/68. Urine contains three plus albumin, hyaline and granular casts.

Blood Chemistry—Urea nitrogen, 15.4 mg per hundred c c , incoagulable nitrogen, 35.8 mg per hundred c c , uric acid, 2.4 mg per hundred c c , creatinin, 1.3 mg per hundred c c , cholesterol, 0.320 per cent, total serum protein, 4.3 per cent. Basal metabolism 33.4 calories, —15 per cent.

The findings in this case are of special interest because they indicate that the depression in basal metabolism is not dependent on the presence of edema, but is one of the essential phenomena in this disease.

CASE 6—History—Frank S., aged 36, had a pulmonary tuberculosis of seven years' duration. For the last seven months there had been generalized edema, dyspnea and gastric distress.

Examination—Extensive bilateral pulmonary involvement, marked edema. Blood pressure 125/80. The urine contained large amounts of albumin, hyaline and granular casts. The phenolsulphonephthalein output was 25 per cent in two hours.

Blood Chemistry—Urea nitrogen, 18.2 mg per 100 c c , incoagulable nitrogen, 38.5 mg per hundred c c , uric acid, 1.7 mg per hundred c c , creatinin 1.3 mg per hundred c c , cholesterol, 0.484 per cent. Basal metabolism 44.2 calories, +12 per cent (afebrile course).

Sputum positive for tubercle bacilli.

Treatment—This case was at first considered one of nephrosis and the patient was put on a high protein diet for two weeks with no improvement. The case was then complicated by the development of a tuberculous otitis media and mastoiditis. When this subsided, the patient was put on a Kairrell diet. Within three days there was a diuresis and the edema disappeared within two weeks on a restricted diet. There was no elevation of temperature to account for the slightly increased basal metabolism.

CASE 7—History—Yetta R., aged 28, had scarlet fever in childhood. This was a typical case of chronic diffuse nephritis with slight edema. Blood pressure 145/100. Hemoglobin, 29 per cent, erythrocytes, 1,800,000. The urine contained albumin three plus, many hyaline and granular casts.

Blood Chemistry—Urea nitrogen, 82.6 mg per hundred cc, incoagulable nitrogen, 146.7 mg per hundred cc, uric acid, 9 mg per hundred cc, creatinin, 8.8 mg per hundred cc, cholesterol, 0.290 per cent Basal metabolism 37.6 calories, normal

Course—An attempt to relieve the edema with the high protein feeding was unsuccessful. Other measures were also of no aid. The patient left the hospital unimproved.

CASE 8—History—Peppie W, aged 54, for several months noticed failing vision, nocturia and weakness. Blood pressure 180/95. No edema. Albuminuric retinitis. Phenolsulphonephthalein output was 45 per cent in two hours. The urine contained albumin two plus, hyaline and granular casts.

Blood Chemistry—Urea nitrogen, 18.2 mg per hundred cc, incoagulable nitrogen, 52.5 mg per hundred cc, uric acid, 1.7 mg per hundred cc, creatinin, 1.1 mg per hundred cc, cholesterol, 0.412 per cent Basal metabolism 38.6 calories, +6 per cent.

Course—The patient's condition remained unchanged on a restricted diet and she was discharged unimproved.

CASE 9—History—Isadore T, aged 48. Past history of no importance. Present illness began six months ago with severe frontal and occipital headaches, vertigo and anorexia.

Examination—Cardiac hypertrophy. Blood pressure 235/130 and 244/135. The urine contained a faint trace of albumin and hyaline casts, specific gravity ranged between 1.016 and 1.022. The phenolsulphonephthalein excretion was 25 per cent in two hours.

Blood Chemistry—Urea nitrogen, 16.8 mg per hundred cc, incoagulable nitrogen, 6.4 mg per hundred cc, uric acid, 3.5 mg per hundred cc, creatinin, 2.3 mg per hundred cc, cholesterol, 0.254 per cent Basal metabolism 41 calories, +6 per cent.

Course—The patient was put on a restricted diet with little change in his condition.

CASE 10—History—Hyman B, aged 39. Nephritis eleven years ago and again six years ago. For the past three weeks there has been generalized edema of moderate degree accompanied by severe headaches, partial blindness and lumbar pain.

Examination—Albuminuric retinitis, cardiac hypertrophy. Blood pressure 220/140. The urine contained a trace of albumin, hyaline and granular casts. The specific gravity was 1.010. The phenolsulphonephthalein excretion was 3 per cent in two hours.

Blood Chemistry—Urea nitrogen, 36.4 mg per hundred cc, incoagulable nitrogen, 73.7 mg per hundred cc, uric acid, 3.3 mg per hundred cc, creatinin, 5.2 mg per hundred cc, cholesterol, 0.140 per cent Basal metabolism 41 calories, +6 per cent.

Course—There was no change in the condition of this patient while on a restricted diet.

Case 10 is unquestionably one of chronic interstitial nephritis and shows a normal basal metabolic rate. The first five cases are true nephroses and show a definitely decreased basal metabolism. The edema in Case 1 cleared up on a high protein diet and thyroid therapy after all other methods of relief had failed. Rose B (Case 2) showed a remarkable diuresis following high protein and thyroid. The basal metabolism returned to normal coincident with the clinical improve-

ment, but the blood cholesterol remained practically unchanged. In spite of a 4 plus Wassermann, antisyphilitic treatment only aggravated the condition.

Esther S (Case 3) at first showed no improvement with the high protein diet, low salt and low protein diet, restricted fluids and diuretics. Then, when thyroid was given in combination with a high protein diet, a remarkable diuresis followed, with rapid disappearance of the edema, and a loss of 23 pounds in four weeks. In this case, apparently, the patient was unable to utilize adequately the protein given until thyroid was administered.

Maude E (Case 4) presented a typical case of nephrosis which at first responded to a high protein diet and small doses of thyroid. The subsequent relapse, we believe, was due to insufficient thyroid dosage or utilization. This case is still under observation.

Ira S (Case 5) had a nephrosis in the nonedematous stage. The reduced basal metabolism and the chemical findings characteristic of this type of disease were present. This is of particular significance as it demonstrates that the lowered metabolism in this condition is not due to tissue dilution.

Isadore T (Case 9) had an essential hypertension with secondary nephrosclerosis. The blood chemistry indicates moderate nitrogen retention and slight increase in cholesterol. The basal metabolism is normal.

Peppie W (Case 8) and Yetta R (Case 7) had a chronic diffuse nephritis. The blood chemistry is, in the main, like that of the hypertensive types of nephritis (chronic diffuse nephritis and nephrosclerosis) differing only in the presence of a hypercholesterinemia. We believe that the high blood cholesterol may be due to a lipid mobilization following the loss of much albumin through the kidney, and therefore does not indicate necessarily a primary metabolic disorder. This is supported by the fact that the basal metabolism in these cases is normal.

Frank S (Case 6) was regarded as having a nephrosis with a slightly increased basal metabolism. Here we have the complicating factor of tuberculosis. The failure of the high protein diet and thyroid therapy in addition to the increased basal metabolic rate suggests that this condition has a tuberculous basis, and that the nature of the renal disturbance was that of an amyloid kidney.

In 1917 Aub and DuBois³ reported metabolic studies on ten cases of nephritis. Five of these were diagnosed as chronic interstitial nephritis and showed normal metabolic rates corresponding to our findings. The remaining cases of their group were diagnosed as chronic parenchymatous nephritis with edema and may be summarized as follows:

JOSEPH U, scarlet fever five years before entrance Generalized edema for three weeks previous to admission The urine contained albumin three plus, hyaline, granular and pus casts The blood pressure was 175/108-149/84 The blood chemistry Urea nitrogen, 57.4 mg per hundred cc, incoagulable nitrogen, 100 mg per hundred cc, creatinin, 191 mg per hundred cc Basal metabolism varied from -7 to +14 per cent

The patient did well on a mixed diet of 1,500 calories, 5 gm nitrogen, and hot air baths Edema disappeared almost entirely Was doing well when he suddenly became ill, developed pneumonia and died eleven days after the onset of the infection

WILLIAM S, aged 27, for one year had a recurring edema There was marked edema at entrance The urine contained large amounts of albumin, hyaline and granular casts Blood pressure, 178/90 The blood chemistry Urea nitrogen, 17.3 mg per hundred cc, nonprotein nitrogen, 41.7 mg per hundred cc Basal metabolism, +4 per cent

The patient improved steadily on a restricted diet

ADAM P, aged 26 history of rheumatic fever The urine contained large amounts of albumin, hyaline and granular casts There was marked generalized edema The blood pressure was 200/130 The blood chemistry Urea nitrogen, 34.3 mg per hundred cc, creatinin 0.5 mg per hundred cc, uric acid, 37 mg per hundred cc Basal metabolism ranged from -10 to -13 per cent

The patient improved on a restricted diet and hot air baths, with the disappearance of the edema within three weeks

LEE H, aged 21 Past history was not obtained Marked edema was present The urine contained albumin three plus many hyaline and granular casts The blood pressure was 115/80 The blood chemistry Urea nitrogen, 32 mg per hundred cc, creatinin, 0.84 mg per hundred cc Basal metabolism, -13 per cent

This patient was put on a restricted diet, the edema continued to increase, the weight increased, and the basal metabolism dropped to -27 per cent The patient died and postmortem aspiration of the pleural cavity and abdomen yielded a milky fluid containing very few cells

EDNA S, aged 13, history negative except for mild sore throat There was marked generalized edema Blood pressure 145/105 The urine contained large amounts of albumin and many hyaline and granular casts The blood chemistry Urea nitrogen, 14.5-22.6 mg per hundred cc, nonprotein nitrogen, 19.7 mg per hundred cc Basal metabolism -40 per cent

A restricted diet low in nitrogen was of no benefit The edema steadily increased and the patient died

No lipid studies were made in these cases

It will be noted that in the three cases with normal metabolic rates the edema disappeared on restricted diets In the two cases with marked decrease in basal metabolism, the edema steadily increased on restricted diets and both patients died We believe that these two cases of Aub and DuBois correspond to our Cases 1, 2 and 3, which we regard as cases of true nephroses and which have yielded to high protein therapy That our assumption of a respiratory quotient of 0.82 does not invalidate our basal metabolic determination in these cases is also shown by those observers In twelve of their fourteen observations on nephritis the respiratory quotient ranged from 0.78 to 0.84 In only two cases were there abnormal values and these patients were on carbohydrate diets

Basal metabolism studies on this group of cases have been undertaken only recently, and because of this, the number of cases reported is still relatively small. However, they gain added significance from the results of thyroid therapy recently reported by Epstein,⁴ Eppinger,⁵ Volhard⁶ and others, in the treatment of various forms of edema, particularly waxy edemas, and others in which the factor of protein deficiency enters. The cases reported above show that those which respond to protein therapy are accompanied by a subnormal basal metabolism. This seems to us to be a logical finding in view of the associated defective protein metabolism, and may be explained by the diminution of the specific dynamic energy normally imparted by the products of protein catabolism. In this way the basal metabolism determination serves as an indirect measure of the protein deficiency, and may be an added diagnostic and therapeutic index of considerable value. That the beneficial effect of thyroid is due entirely to its stimulative influence on basal metabolism is open to question, and it is quite probable that its effect in promoting the utilization of exogenous and endogenous protein, as demonstrated by Magnus-Levy, von Norden et al., explains its action. This phase of the subject, however, is still a matter for further investigation, but that a low metabolic rate in itself is not sufficient to cause edema is shown by the following two cases.

CASE 11—Arthur S., aged 20, a psychopath who on a self-imposed low calory, low protein diet reduced his weight from 146 to 73 pounds.

Basal metabolism 227 calories, —42 per cent. Blood cholesterol 0.102 per cent.

CASE 12—Rose Y., aged 21, a cretin, on thyroid therapy and under observation for fifteen years. Symptoms entirely neurologic.

Basal metabolism 32 calories, —15 per cent. Blood cholesterol 0.130 per cent.

Neither of these patients developed at any time either edema or myxedema. It will be noted that these are the only two instances in which a low metabolic rate is associated with a low blood cholesterol, indicating the importance of increased lipoids as an accessory factor in edema. In these cases with a low basal metabolism the protein utilization is apparently unimpaired, a factor considered by Rubner as significant in the prevention of edema in cases of starvation. Further, it is of interest to note that in hyperthyroidism, a condition in which emaciation of great degree may occur, but in which the basal metabolism and protein utilization are increased, edema is practically never encountered.

In Table 6 ten menopause cases are reported. All have normal basal metabolic rates, but the blood cholesterol figures range from 0.182 to 0.394 per cent. The tendency to a hypercholesterinemia is noted in these cases. In this connection we wish only to point out the importance of the climacteric period as a factor in the elevation of blood

TABLE 6—MENOPAUSE CASES

Acc No	Name	Age	Date	Basal Metabolism		Blood Cholesterol, Per Cent
				Calories	Per Cent	
208950	A M	42	April 15	42	+15	0 182
208982	G L	47	Mar 31	40	+12	0 230
208949	Y A	40	Mar 31	37 8	+ 3	0 192
209157	S K	48	April 7	39 8	+10	0 248
209174	O B	45	April 7	40	+10	0 220
209242	A R	40	April 11	38	+ 4	0 206
209169	E F	47	April 18	36	Normal	0 394
209561	A F	45	April 21	36 5	Normal	0 182
209671	H W	45	April 25	37 5	+ 4	0 240
209648	Y R	42	April 25	37	Normal	0 242

cholesterol, so that no false conclusions will be drawn in cases at this age with subnormal basal metabolism

In Table 7 are recorded conditions in which either the blood cholesterol or the basal metabolism is subject to variation. These cases are too few to permit the drawing of any conclusions, but it will be seen that the inverse relationship between basal metabolism and blood cholesterol holds true in most of them, with the exception of the blood conditions

TABLE 7—MISCELLANEOUS GROUP

Acc No	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent	Diagnosis
					Calories	Per Cent		
211699	B E	20	♀	Oct 21	37 8	Normal	0 218	Cholelithiasis
205390	D R	35	♀	Nov 10	37 5	Normal	0 178	Cholelithiasis
205132	S K	49	♀	Oct 23	36	Normal	0 130	Pernicious anemia
205503	A M	49	♀	Dec 2	43	+10	0 236	Lymphatic leukemia
208909	S K	30	♀	Mar 29	42 5	+ 7	0 084	Polycythemia vera
207396	B A	42	♀	Feb 15	38 6	+ 6	0 284	Obesity
204394	L C	19	♀	Oct 2	35	- 8	0 303	Hypopituitarism and glycosuria
208255	O H	25	♀	Mar 12	40	+ 6	0 160	Achondroplasia
208109	M B	42	♀	Mar 3	36 4	Normal	0 174	Splenomegaly with anemia
206713	H G	17	♀	Dec 28	55	+32	0 100	Gaucher splenomegaly

DISCUSSION

The material presented, we believe, shows that the relationship existing between the metabolic rate and the blood cholesterol in thyroid disease is more than an incidental one. The low blood cholesterol values with an increased metabolic rate and the high values with a depressed basal metabolism, lead one naturally to believe that it may be only a matter of combustion, an increased rate of oxidation causing increased consumption of available lipid, and vice versa. We do not believe that this is the complete explanation. However, until more is known about the metabolism of lipoids in the body, any explanation must be based on hypotheses, as yet incapable of proof. The more recent work of Marine and Bauman,⁸ in which they demonstrated a

8 Marine, D., and Bauman, E. J. *Am J Physiol* 57 135, 1921

rise in basal metabolism following the destruction of the supra-renal cortex in rabbits, is especially suggestive, in the light of the close relationship existing between the supra-renal cortex and the blood cholesterol. Marine and Bauman suggest that the supra-renal cortex may have an inhibitory function in the regulation of basal metabolism. The possibility exists that such a power may be inherent in its lipid content which is known to vary with that of the blood.⁹ In Addison's disease, for example, the blood cholesterol is very low. It is also known that in fatal cases of exophthalmic goiter the lipid content of the supra-renal cortex is greatly reduced.

Wasting diseases other than hyperthyroidism are associated with a low blood cholesterol. The diagnostic value of a low cholesterol is doubtful, but a normal or elevated figure must be a rare finding in exophthalmic goiter. In enlargements of the thyroid with toxic symptoms the lipid content may be out of proportion to the metabolic rate, but this is explained by the menopause factor which tends to give a higher initial figure. Once established in connection with the basal metabolic rate, we believe that repeated cholesterol determinations offer a satisfactory method of following the course of thyroid toxicity. This is of special value in judging the effect of thyroid therapy in myxedema and allied conditions of hypothyroidism. It is known that in some cases of hyperthyroidism, the basal metabolism does not correspond to the severity of the condition as observed clinically. This is to be expected as the damage to the myocardium, nervous system and body reserve outlasts the elevation of the metabolic rate. We believe that in these cases the blood cholesterol, as an index of the lipid content of the supra-renal cortex and body tissue, may be of considerable value in prognosis, and as an indication of the safety of operative procedure. It is worth noting that the patient with a blood cholesterol of 0.095 per cent died on the operating table.

In nephrosis, we believe basal metabolism determinations will prove to be of great value in differentiating cases suitable for high protein and thyroid therapy. The subnormal metabolism found in these cases is not necessarily due to a hypothyroidism but to defective protein metabolism, with its associated diminution of the specific dynamic energy normally imparted by products of protein catabolism. In this way the basal metabolism determinations serve as an indirect measure of protein deficiency. We believe that the beneficial effect of thyroid is not due entirely to its stimulative action on the rate of oxidation, as a subnormal metabolism in itself is not sufficient to produce edema. The effect of thyroid in promoting the utilization of protein probably explains its ultimate influence on edema.

THE DISTRIBUTION OF METABOLITES IN THE BLOOD AND TISSUES*

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MINNEAPOLIS

INTRODUCTION

With the introduction of simple and reliable microchemical methods of analysis, the determination of the concentration of metabolites in the blood has become an accepted clinical procedure. Consequently, the relation of metabolites in the blood to their distribution throughout the entire organism is a subject of clinical as well as theoretic interest. I wish here to consider the distribution of metabolites in the body as a whole in relation to their concentration in the blood.

Three methods have been applied in studying metabolite distribution. The first, which is used in this report, consists in parallel determinations of the metabolites in the blood and in the various body fluids. The second method consists in the postmortem analyses of tissues to determine their respective metabolite content. The third method is the study of the effect produced by the ingestion of a given quantity of meat, or urea, and the resultant changes in the blood metabolites, controlling the experiments with nitrogen excretion determinations. The limitations of each of these three methods will be discussed later.

The first parallel analyses of urea were made by Javal and Adler¹ in 1906, using the hypobromite method. In four cases they found the urea content of different fluids from the same cases in practical accord. Javal and Boyet² reported ten cases with a similar agreement in 1910. In 1911, Javal³ made parallel urea estimations on the blood and cerebrospinal fluid in eighteen cases, blood and edema fluid in four cases, pleural and edema fluid in one case, blood and pleural fluids in five cases, and pleural and cerebrospinal fluids in five cases. The urea concentrations in the fluids from the same cases were virtually identical. Javal concluded that "when the urea increases in the serum it also increases simultaneously in the organism and diffuses through all the fluids of the organism in the same concentration in which it occurs in the serum. The blood contains from 30 to 35 mg

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1 Javal and Adler. *Seances et Mém de la Soc de Biol* **61** 235, 1906.

2 Javal and Boyet. *Ibid* **68** 527, 1910.

3 Javal. *J de phys et de path gen* **13** 508, 1911.

urea nitrogen per hundred cubic centimeters. Normally, the cerebrospinal fluid contains about the same quantity." Javal's figures are approximately twice those now considered normal for blood urea nitrogen, doubtless because the hypobromite method used gives nitrogen other than urea nitrogen added to the true urea nitrogen figure.⁴

Rosenberg,⁵ in 1914, made parallel determinations of urea, creatinin and indican in the blood and in the ascitic, pleural, and cerebrospinal fluids of nephritics. He also used the hypobromite urea method. Normal subjects were not studied. Rosenberg concludes that "in uremia, the urea content of the pleural and peritoneal fluids is from 80 to 100 per cent of the blood. The creatinin content is up to 20 per cent of the blood, and the indican is equal to the blood. The cerebrospinal fluid contains from 56 to 96 per cent of the urea content of the blood, and from 37 to 75 per cent of the blood creatinin." With the exception of considerably higher creatinin percentages for the body fluids, these findings coincide with those reported here. Using modern microchemical methods, Bernhard⁶ found the nonprotein nitrogen, urea nitrogen, sugar and chlorides in eleven transudates and exudates to be comparable to those of normal blood. He did not make parallel analyses of the blood at the same time, and does not state whether or not the fluids were obtained with the patient in the fasting state.

The sugar content of transudates and exudates compared to the sugar content of the blood at the same time has been studied by Hagler and Schumann,⁷ using the method of Bang. Of six pleural transudates, all but one had as high a sugar content as the blood, or higher. In twenty pleural exudates, the sugar content was usually lower than that of the blood, in eight peritoneal transudates it was slightly higher, and in seven cases of peritonitis it was slightly lower than the normal blood sugar. The ingestion of 100 gm levulose or dextrose caused parallel increases in the sugar content of blood and fluids. From parallel analyses on the blood and fluids in five cases with pleuritic, and four cases with ascitic effusions, Dennis and Minot⁸ conclude that the urea, uric acid, creatinin and nonprotein nitrogen occur in the same concentration in exudates and transudates as in the blood. They found the sugar content of the four ascitic fluids somewhat higher than that of the blood, contrary to the pleuritic fluids, which had a somewhat lower sugar content.

4 Herter and Wakeman. *J. M. Research* **4** 119, 1899, *Johns Hopkins Hosp. Rep.* **9** 69, 1900.

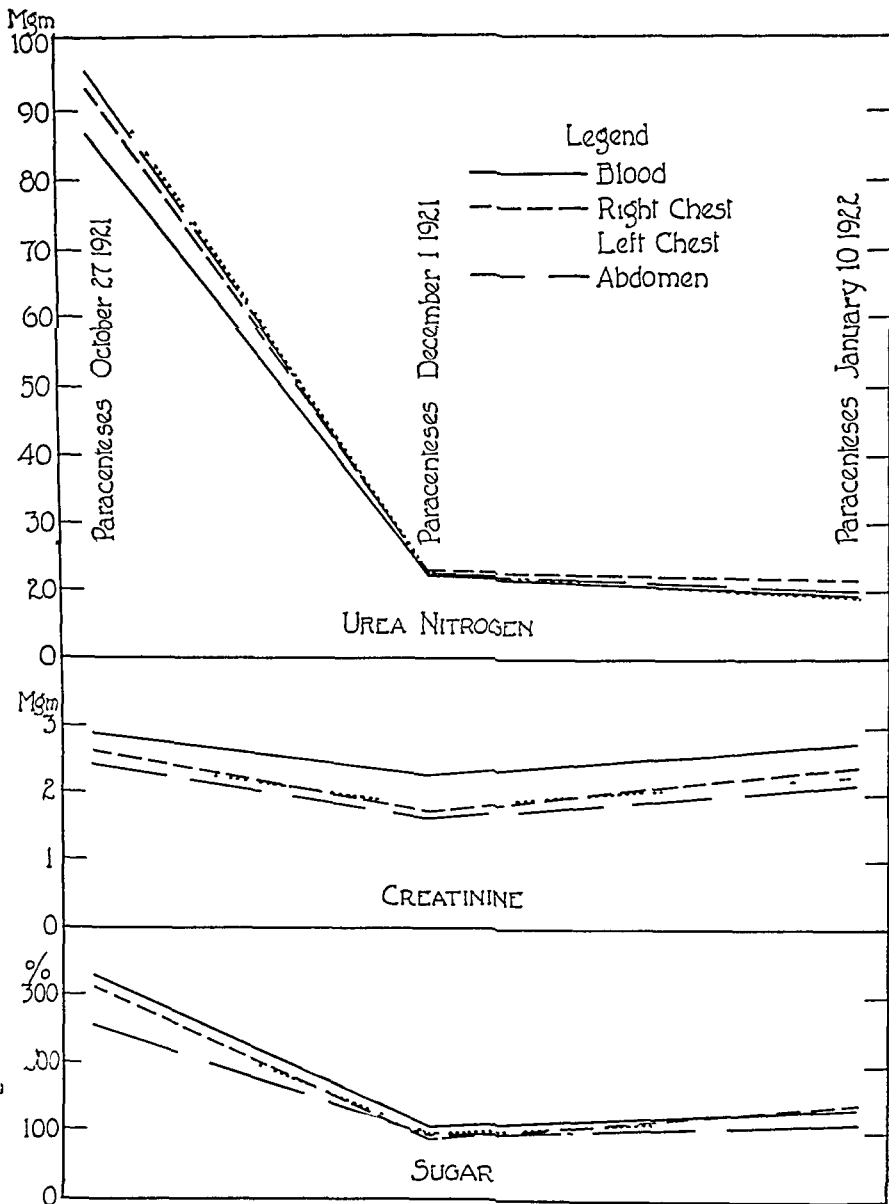
5 Rosenberg. *Berl. klin. Wchnschr.* **49** 1314, 1916.

6 Bernhard. *Interstate M. J.* **49** 188, 1918.

7 Hagler and Schumann. *Med. Klin.* **9** 1810, 1913.

8 Dennis and Minot. *Arch. Int. Med.* **20** 879 (Dec.) 1917.

Seham and Nixon⁹ have recently investigated the chemistry of normal and pathologic spinal fluids. Their complete summary of the extensive literature makes further citation unnecessary. They report an average spinal fluid sugar content of 56.2 per cent of the blood sugar in



Case of chronic nephritis illustrating parallel distribution of urea nitrogen, creatinin and sugar in the blood, ascitic fluid and right and left pleural effusions

normal cases, with a maximum of 70.3 per cent and a minimum of 47.8 per cent. Their findings for sugar are comparable to those of previous investigators. In four normal subjects they found the spinal fluid

⁹ Seham and Nixon. Arch. Int. Med. 28:561 (Nov.) 1921

creatinin to average 95.5 per cent of the blood creatinin, and the diseases with high blood creatinin exhibited a corresponding increase in the creatinin content of the spinal fluid. In four normal subjects the urea content of the spinal fluid averaged 62.15 per cent of the blood urea, with a range of from 45.5 to 174.6 per cent in pathologic cases. Their findings for urea differ from those of Cullen and Ellis,¹⁰ who report almost complete agreement between the urea content of the spinal fluid and the blood. Meyers and Fine¹¹ found in nephritics that the former averages 88 per cent of the latter. The figures of Selham and Nixon are somewhat higher for spinal fluid creatinin, and somewhat lower for urea, than those reported in this paper.

The various investigators of the metabolite distribution between the blood and other body fluids thus appear in fairly close agreement. They find both the nitrogenous metabolites and the sugar in approximately the same concentration in fluids and in blood. The percentages for the blood are usually slightly higher than for the other fluids, but an increase in the blood values appears to be associated with corresponding increases in the values in the fluids.

PROCEDURE

This study is concerned with further investigation of the distribution of metabolites between the blood and other body fluids, primarily in cases in which the blood exhibits no retention of metabolites. A few cases with increased retention are included for comparison.

In all cases the blood and fluids were obtained simultaneously. The patients were kept without food overnight, and the samples were obtained before breakfast, Jacobsen and Edwards¹² having shown that there may be an increase in blood urea, as well as blood sugar, following the ingestion of an ordinary meal. The specimens were immediately sent to the laboratory, where parallel determinations of the sugar, urea nitrogen and creatinin were done. Most of the determinations were made in less than half an hour after withdrawal of the fluids from the patient. The analyses were all made by the same person. Double estimations on the same specimen were frequently made to check the technic, with results well within the limits of experimental error. Urea nitrogen was estimated by Van Slyke and Cullen's modification of Marshall's urease method,¹³ creatinin by the method of Folin,¹⁴ sugar by the method of Lewis and Benedict.¹⁵ A Kober colorimeter was

10 Cullen and Ellis *J Biol Chem* **20** 511, 1915

11 Meyers and Fine *J Biol Chem* **37** 239, 1919

12 Jacobsen and Edwards *Am J M Sc* **159** 579, 1920

13 Van Slyke and Cullen *J Biol Chem* **24** 117, 1916

14 Folin *J Biol Chem* **17** 475, 1914

15 Lewis and Benedict *J Biol Chem* **20** 61, 1915

employed The percentage concentration of the metabolites in each fluid was obtained by dividing the concentration of the metabolite in the fluid, times 100, by the concentration of the metabolite in the blood

CLASSIFICATION OF MATERIAL

In all, fifty-five fluids from thirty-six cases were analyzed As often as possible, more than one fluid was obtained from the same case Several cases were used more than once, but at each fluid determination a parallel blood analysis was done at the same time The

TABLE 1—CLASSIFICATION OF CASES ACCORDING TO GROUPS

Group		Cases
I	Effusions in cases with normal blood metabolites	31
	Ascitic transudates	13
	Thoracic transudates	7
	Ascitic exudates	4
	Thoracic exudates	7
II	Effusions in cases with increased blood metabolites	4
	Ascitic transudates	1
	Thoracic transudates	3
III	Cerebrospinal fluids in cases with normal blood metabolites	15
	Normal fluids	7
	Pathologic fluids	8
IV	Cerebrospinal fluids in cases with increased blood metabolites	5
	Normal fluid	1
	Pathologic fluids	4
Total		55

TABLE 2—GROUPING OF FLUIDS ACCORDING TO CLINICAL DIAGNOSES

Diagnosis	Cases	Diagnosis	Cases
Chronic nephritis	10	Polyserositis	1
Hepatic cirrhosis	9	Acute peritonitis	1
Carcinoma	4	Acute pericarditis	1
Tuberculous pleurisy	4	Cholecystitis	1
Tabes dorsalis	3	Neurasthenia	1
General paresis	3	Dementia præcox	1
Myocardial degeneration	2	Neurosyphilis	1
Tuberculous peritonitis	2	Lethargic encephalitis	1
Empyema	2	Cerebrospinal meningitis	1
Hysteria	2	Uremia	1
Aneurism	1	Alcoholism	1
Hydrocele	1	Normal	1
Total			55

cases have been arranged in four groups (Table 1) The clinical diagnoses are arranged in Table 2

EXPERIMENTAL RESULTS

The results of the determinations are given in Tables 3 to 8, and for comparison the average figures for each group are arranged in Table 7 In the cases with normal blood metabolite concentration, the sugar content of the ascitic transudates averaged 96.47 per cent of the blood sugar, with a minimum of 51 per cent and a maximum of 112 per cent In the same cases the average ascitic urea nitrogen was 95.90 per cent of the blood urea nitrogen, with a minimum of 60

per cent and a maximum of 180 per cent. In this group the percentage of creatinin averaged somewhat less, from 67.31 per cent, with a minimum of 30 per cent and a maximum of 91 per cent of the blood creatinin. The averages for the corresponding group of thoracic transudates, in cases with normal blood metabolites, was quite similar. In this

TABLE 3—GROUP I. A. ASCITIC AND THORACIC TRANSUDATES WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent	Blood	Fluid	Per Cent	Blood	Fluid	Per Cent
1	Ascitic	Carcinomatosis	0.096	0.102	106.25				1.844	1.600	86.00
2	Ascitic	Carcinomatosis	0.104	0.080	76.90	17.85	14.00	78.00	1.416	0.435	30.00
3	Ascitic	Hepatic cirrhosis							1.700	1.250	73.00
4	Ascitic	Hepatic cirrhosis	0.086	0.071	82.50	14.00	9.10	65.00	1.790	1.610	91.00
5	Ascitic	Hepatic cirrhosis	0.093	0.095	102.00	17.85	14.35	79.00	1.950	1.540	78.00
6	Ascitic	Hepatic cirrhosis	0.114	0.105	92.00	10.85	12.60	116.00	1.820	1.000	54.92
7	Ascitic	Hepatic cirrhosis	0.109	0.165	60.00	28.70	28.00	97.50	2.000	1.170	58.50
8	Ascitic	Hepatic cirrhosis	0.123	0.071	51.00	11.55	20.90	180.00	1.807	1.110	61.00
9	Ascitic	Gastric carcinoma	0.100	0.096	96.00	11.80	11.90	100.00	1.860	1.570	84.00
10	Ascitic	Hydrocele	0.102	0.087	85.00	5.25	3.15	60.00	2.360	1.500	63.50
11	Ascitic	Hepatic cirrhosis	0.083	0.093	112.00	9.10	7.14	78.40	1.180	1.400	77.70
12	Ascitic	Hepatic cirrhosis	0.081	0.088	108.00	8.65	8.05	92.80	1.280	1.100	81.00
13	Ascitic	Chronic nephritis	0.100	0.096	96.00	23.00	23.10	100.00	2.250	1.760	78.20
Av	Ascitic		0.099	0.096	96.47	14.43	13.84	95.90	1.953	1.318	67.31
1	Thoracic	Chronic nephritis	0.133	0.138	103.76	18.88	21.68	114.30	2.770	2.380	85.90
2	Thoracic	Aneurysm of arch	0.098	0.079	80.60	14.00	13.65	97.50	2.110	1.310	62.56
3	Thoracic	Chronic nephritis	0.100	0.086	86.00	23.00			2.250	1.730	76.80
4	Thoracic	Chronic nephritis	0.100	0.088	88.00	23.00	23.80	100.30	2.250	1.700	79.40
5	Thoracic	Myocardic degeneration	0.112	0.091	81.20	15.05	8.40	55.70	1.630	1.110	66.60
6	Thoracic	Myocardic degeneration	0.094	0.082	87.20	14.00	5.25	37.50	1.760	1.320	75.00
7	Thoracic	Chronic nephritis	0.133	0.127	95.48	18.88	18.60	98.64	2.770	2.307	81.00
Av	Thoracic		0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
Average			0.104	0.098	94.23	16.27	13.30	89.30	2.089	1.512	72.38

group the average sugar content of the fluid was 90 per cent, with a minimum of 80.6 per cent and a maximum of 103.76 per cent. The urea nitrogen averaged 84.09 per cent, with a minimum of 37.5 per cent and a maximum of 114.3 per cent of the blood urea nitrogen. The creatinin averaged 76.89 per cent with a minimum of 62.56 per cent and a maximum of 85.9 per cent (Table 3).

The corresponding exudates showed slightly lower percentages than the transudates. The sugar content of the ascitic transudates with normal blood metabolites averaged 75.55 per cent, with a minimum of 59 per cent and a maximum of 98 per cent. The urea nitrogen averaged 70.02 per cent, with a minimum of 41 per cent and a maximum of 113 per cent. The creatinin averaged 48.8 per cent, with a minimum of 35 per cent and a maximum of 72 per cent. In the corresponding group of thoracic exudates, the sugar content averaged 79.32 per cent, with a minimum of 0 (case of acute empyema), and a maximum of 106.9 per cent. The urea nitrogen in this group averaged

TABLE 4—GROUP I B ASCITIC AND THORACIC EXUDATES WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent	Blood	Fluid	Per Cent	Blood	Fluid	Per Cent
1	Ascitic	Tuberculous peritonitis	0.114	0.075	65.00	12.78	5.33	41.00	2.000	0.900	45.00
2	Ascitic	Tuberculous peritonitis	0.126	0.075	59.00	29.65	14.89	50.00	2.550	1.200	47.00
3	Ascitic	Polyserositis	0.102	0.084	82.00	23.55	22.42	95.00	2.850	1.000	35.00
4	Ascitic	Acute peritonitis	0.108	0.106	98.00	8.65	9.80	113.00	2.080	1.500	72.00
Av	Ascitic		0.113	0.085	75.55	18.66	13.11	70.02	2.370	1.150	48.80
1	Thoracic	Empyema	0.088	0.000	00.00				2.000	1.400	70.00
2	Thoracic	Tuberculous pleurisy	0.083	0.087	104.80	24.05	22.05	91.69	1.740	1.730	99.90
3	Thoracic	Tuberculous pleurisy	0.098	0.102	104.10	28.70	21.30	73.17	2.500	2.050	82.00
4	Thoracic	Tuberculous pleurisy	0.095	0.097	102.20	12.60	13.60	104.00	2.110	1.780	84.32
5	Thoracic	Tuberculous pleurisy	0.101	0.108	106.90	22.20	18.20	81.90	1.880	1.760	93.61
6	Thoracic	Empyema, lues	0.160	0.096	60.00	13.30	10.15	76.31	2.330	1.600	69.53
7	Pericardial	Acute pericarditis	0.100	0.086	86.00	14.00	12.46	89.00	2.000	1.410	70.50
Av	Thoracic		0.103	0.082	79.32	19.14	16.29	86.01	2.066	1.621	78.41
Average			0.108	0.083	77.93	18.90	14.70	78.01	2.212	1.385	62.16

86.01 per cent, with a minimum of 73.17 per cent and a maximum of 100 per cent. The creatinin figures averaged 78.41 per cent, with a minimum of 69.53 per cent and a maximum of 99.9 per cent (Table 4).

The cerebrospinal fluids in cases with normal blood metabolite concentration show consistently lower percentages of metabolites. The figures for the normal and pathologic fluids yield remarkably similar figures. The spinal fluid sugars averaged 60.21 per cent, with a minimum of 40.1 per cent and a maximum of 89.6 per cent. In the same group the spinal fluid urea nitrogen averaged 66.5 per cent, with a

minimum of 39.9 per cent and a maximum of 140 per cent. The creatinin averaged 59.8 per cent, with a minimum of 22.03 per cent and a maximum of 90 per cent (Table 5).

Although the bloods from the group of cases with increased metabolite concentration show a decided rise above the normal blood

TABLE 5—GROUP III NORMAL AND PATHOLOGICAL CEREBROSPINAL FLUIDS WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent	Blood	Fluid	Per Cent	Blood	Fluid	Per Cent
1	Normal	Cholecystitis	0.102	0.055	53.93	12.60	4.65	39.90	1.148	0.253	22.03
2	Normal	Neurasthenia	0.092	0.063	68.48	13.65	8.60	63.00	0.968	0.343	35.33
3	Normal	Gastric carcinoma	0.080	0.037	46.45				1.800	1.300	73.33
4	Normal	Cirrhosis	0.074	0.055	74.32				2.340	1.360	58.12
5	Normal	Hysteria	0.087	0.052	60.00				1.807	1.310	71.80
6	Normal	Dementia præcox	0.097	0.064	66.00	9.80	8.30	84.50	1.720	1.210	70.30
7	Normal	Normal	0.073			10.85	7.00	64.00	2.000	1.200	60.00
Av	Normal		0.086	0.054	61.53	11.73	7.16	61.00	1.683	0.997	59.20
1	Path	Neurosyphilis	0.102	0.041	40.10	18.80	9.80	51.60	1.820	1.200	66.00
2	Path	General paresis	0.166	0.084	50.60	20.30	9.80	48.27	2.000	1.470	73.50
3	Path	Tabes dorsalis	0.102	0.050	49.00				0.960	0.880	71.66
4	Path	Enceph. letharg.	0.125	0.074	59.30				1.416	0.843	24.18
5	Path	General paresis	0.093	0.050	53.76	11.20	15.70	140.00	1.500	0.340	22.80
6	Path	General paresis	0.105	0.060	57.14	13.48	7.64	56.60	1.000	0.900	90.00
7	Path	Tabes dorsalis	0.155	0.139	89.60	19.90	16.80	84.42	1.870	1.310	70.00
8	Path	Tabes dorsalis	0.097	0.055	56.50	7.77	4.90	63.69	1.780	1.030	59.90
Av	Path		0.118	0.069	58.90	15.24	10.77	70.60	1.543	0.935	60.60
Average			0.102	0.063	60.21	13.48	8.96	66.50	1.613	0.935	59.80

TABLE 6—GROUP II ASCITIC AND THORACIC TRANSUDATES WITH INCREASED BLOOD METABOLITE CONCENTRATIONS

Case No	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent	Blood	Fluid	Per Cent	Blood	Fluid	Per Cent
1	Ascitic	Chronic nephritis	0.325	0.259	76.00	84.20	96.00	114.00	2.88	2.45	85.00
1	Thoracic	Chronic nephritis	0.107	0.152	111.80				4.22	3.98	94.31
2	Thoracic	Chronic nephritis	0.325	0.308	91.69	84.20	93.00	110.45	2.88	2.61	90.62
3	Thoracic	Chronic nephritis	0.325	0.294	90.46	84.20	97.00	115.20	2.88	2.50	86.11
Av	Thoracic		0.232	0.251	99.70	84.20	95.00	112.00	3.33	3.03	91.10
Average			0.288	0.255	88.30	84.20	95.50	113.00	3.10	2.74	88.20

values, the relative concentration of the metabolites in the fluids remains much the same as in the cases without retention. This indicates a corresponding increase in the metabolite content of the fluids. The average sugar content of the effusions with increased blood metabolites was 88.3 per cent as compared with 90 per cent in the

cases without retention. The urea nitrogen averaged 113 per cent, as compared with 89.3 per cent and the creatinin 88.2 per cent, as compared with 76.89 per cent in the normal group (Table 6).

Similarly, where the blood metabolites are increased, the cerebrospinal fluids show a corresponding increase, so that the percentage concentration remains approximately the same as in the group without retention. This is exclusive of a case of acute meningitis in which no spinal fluid sugar was present. In this group the average sugar content was 27.7 per cent, with a minimum of 0 and a maximum of 98.7 per cent. The urea nitrogen averaged 49.8 per cent, with a minimum of 45.9 per cent and a maximum of 107.9 per cent. The creatinin 73.57 per cent, with a minimum of 39.74 per cent and a maximum of 102.6 per cent (Table 7).

The most significant point shown by the data summarized in Table 8 is the relative uniformity of the findings in the various groups. In

TABLE 7—GROUP IV. NORMAL AND PATHOLOGICAL CEREBROSPINAL FLUIDS WITH INCREASED BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent	Blood	Fluid	Per Cent	Blood	Fluid	Per Cent
1	Normal	Hysteria	0.105	0.069	65.71	27.93	12.78	45.90	3.90	1.35	39.74
2	Normal	Nephritis tabes	0.099	0.046	44.66	28.70	30.80	107.90	2.21	1.64	74.40
3	Normal	Alcoholism	0.112	0.091	80.80	46.80	49.70	106.00			
4	Normal	Uremia	0.165	0.083	98.70				9.74	9.99	102.60
Average	Normal		0.120	0.072	60.00	50.53	31.09	61.10	5.28	4.26	80.09
1	Path.	Cerebrospinal meningitis, tabes, nephritis	0.140	0.000	00.00	107.00	45.6	42.61	3.0	2.11	70.33
Average			0.130	0.036	27.70	78.76	38.34	49.80	4.14	2.073	73.57

general, the concentration of sugar, urea nitrogen and creatinin in the fluids of all the groups tends to approximate 80 per cent of their respective concentration in the blood. The spinal fluids are consistently lower than the effusions, approximating 60 per cent of the blood figures. The concentration of creatinin in all the fluids tends to remain relatively lower than the other metabolites in comparison with their respective blood values.

Of special interest is the fact that in Groups II and IV, in which the blood metabolites are increased, the percentage of metabolites in the fluids in relation to the blood is approximately the same as in the cases with normal metabolite levels. This indicates a definite tendency toward equilibrium in the distribution of metabolites between the blood and fluids. This parallelism is well illustrated in Chart I, which shows the findings from a case of chronic nephritis, with ascites and bilateral hydrothorax. On admission the patient's blood urea nitrogen was

87.2 mg per hundred cubic centimeters, with urea nitrogen values for the pleural effusions and ascitic fluid of 93, 97 and 96 mg per hundred cubic centimeters, respectively. Five weeks later, under dietary treatment and rest in bed, the blood urea nitrogen had dropped to 23 mg, the right pleural effusion to 23.8 mg, the left pleural effusion to 23.8 mg, and the ascitic fluid to 23.1 mg per hundred cubic centimeters, respectively. In another five weeks the blood urea had fallen to 18.8 mg, with corresponding drops to 21.68, 18.60 and 19 mg per hundred cubic centimeters, respectively, in the three fluids. The creatinin and sugar values show equally consistent decreases in the blood and three fluids. Although at the time of the first estimations five liters of fluid were removed, and five and a half liters at the time

TABLE 8—SUMMARY OF RESULTS AVERAGE RELATIVE CONCENTRATION OF METABOLITES IN THE BLOOD AND VARIOUS BODY FLUIDS

Classification of Fluids				Metabolite Determinations								
Blood Metabolites	No Cases	Source	Type	Sugar			Urea Nitrogen			Creatinin		
				Blood	Fluid	Per Cent *	Blood	Fluid	Per Cent *	Blood	Fluid	Per Cent *
Group I Normal	13	Ascitic Thoracic	Trans	0.099	0.096	96.17	11.13	13.81	95.90	1.958	1.378	67.31
	7		Trans	0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
	4	Ascitic Thoracic	Fluid	0.113	0.085	75.55	18.86	13.11	70.02	2.370	1.150	48.80
	7		Fluid	0.103	0.082	79.32	19.11	16.20	85.10	2.066	1.621	78.41
Group II Increased	1	Ascitic Thoracic	Trans	0.325	0.259	76.00	81.20	96.00	114.00	2.880	2.450	85.00
	3		Trans	0.252	0.251	99.70	84.20	95.00	112.00	3.326	3.030	91.10
Group III Normal	7	C S Fl	Normal	0.086	0.051	62.70	11.73	7.16	61.00	1.638	0.996	59.20
	8			0.118	0.060	58.80	15.24	10.77	70.60	1.513	0.935	60.60
Group IV Increased	4	C S Fl	Normal	0.120	0.072	60.00	50.53	31.09	61.10	5.280	4.260	80.60
	1			0.110	0.060	60.00	107.00	15.60	42.60	3.000	2.110	70.33
Total	55											

Sugar in per cent urea nitrogen and creatinin in milligrams per 100 c c
Concentration in fluid

* Per Cent = $\frac{\text{Concentration in fluid}}{\text{Concentration in blood}} \times 100$

of the second determination, the metabolite concentration in all the fluids continued to fall. The reaccumulation of effusions appears to bear no relationship to changes in the retention of these metabolites.

No relation between the metabolite figures in the fluids and the clinical diagnoses was apparent.

DISCUSSION

As previously mentioned, there are two other methods for studying the distribution of metabolites in the body. Postmortem analysis of the urea content of various tissues was first employed by Schoendorf¹⁰ in 1899. In a well fed dog he found that the liver, spleen, pancreas and

brain contained approximately the same concentration of urea as the blood (from 0.1115 to 0.1228 per cent), while the heart contained slightly more and the muscle slightly less. Marshall and Davis¹⁷ criticized these findings as being too high for the blood, and probably even less correct for the tissues. They introduced the more accurate urease method of urea estimation, and studied the urea content of normal dogs' tissues postmortem. They found that the percentage of urea was practically constant throughout the body, except the urinary tract, averaging from 28 to 30 mg per hundred grams. Similar results were obtained in postmortem analyses of various human organs. By killing dogs soon after the ingestion of urea per os, they were also able to show that it diffused very rapidly into all the tissues, and whether the urea concentration in the body was normal or increased, it was distributed with remarkable uniformity throughout the various tissues. In similar experiments, Foster and Davis¹⁸ found that the amounts of retained nitrogen could not be accounted for by the total nonprotein nitrogen of the total blood of the body. Postmortem analyses of the tissues led them to conclude that more of the nitrogenous metabolites are retained in the tissues than in the blood. Becker¹⁹ studied the total nonprotein nitrogen in nephrectomized dogs. The relatively greatest increase was in the blood, but the absolutely greatest increase was in the muscles. The increase in the other organs was slight in comparison with the musculature. He found a much closer agreement between the urea nitrogen of the tissues and blood than in the total nonprotein nitrogen. Becker also showed that the increase in total nonprotein nitrogen in the various tissues of dead bodies was related to their respective total nitrogen content, with a fairly constant nonprotein nitrogen total nitrogen ratio of 1:10. Becker states that postmortem analyses of blood nitrogen are more nearly comparable to postmortem tissue analyses than blood analyses obtained antemortem.

Rosenberg²⁰ estimated the metabolites in the blood and thigh muscle of nine normal men, eleven chronic nephritics and seven acute nephritics. The blood was taken either just before or immediately after death, and the thigh muscle as soon as possible postmortem. He extracted the musculature with trichloroacetic acid, and determined the total rest nitrogen by Kjeldahl's method, urea by the hypobromite

17 Marshall and Davis. *J Biol Chem* **18** 53, 1914

18 Foster and Davis. *Proc Soc Exper Biol & Med* **8** 33, 1915

19 Becker. *Deutsch Arch f klin Med* **128** 1 261 1918, *ibid* **129** 1, 8 *ibid* **134** 325, 1920, *ibid* **135** 331 1920. Becker and Strauss. *Zentralbl f Inn Med* **42** 345, 1921

20 Rosenberg. *Arch f exper Path u Pharmacol* **86** 1, 1920, *ibid* **87** 86, 1920 *ibid* **87** 153, 1920

method, creatinin by Folin's method, and indican by the method of Jolles Rosenberg's average figures for normal blood and muscle are as follows

	Blood	Muscle
Rest nitrogen	0.025 per 100 c c	0.307 per 100 gm
Urea nitrogen	0.020 per 100 c c	0.232 per 100 gm
Creatinin	0.0015 per 100 c c	0.00355 per 100 gm

In two cases in which the normal musculature of the thigh was obtained at amputations for disease below the knee, and analyzed immediately, the results were virtually identical with those for muscle analyzed postmortem. Although the hypobromite method which he used gives figures for urea nitrogen approximately twice those obtained by the urease method,⁴ it is difficult to reconcile Rosenberg's figures of 232 mg per 100 gm for the urea content of normal musculature with Marshall and Davis of from 28 to 30 mg per 100 gm. On the other hand, the proportion of rest nitrogen made up of urea nitrogen in Rosenberg's figures is about that generally accepted as normal. His figures for normal blood metabolites, also, are within the generally accepted limits. Rosenberg found similar values for the musculature of rabbits.

From a comparison of the blood chemistry and the postmortem muscle analyses Rosenberg concludes

In uremia the muscle rest nitrogen begins to increase when the blood level rises above 170 mg per hundred cubic centimeters. There is no difference between acute and chronic cases. It is probable that there is a reciprocal relation between the blood and tissues and not, as von Monakow²¹ thought, that the tissues fill with metabolites and then overflow into the blood. In the muscles of chronic nephritics it is found not only that the urea nitrogen increases to a relatively higher degree than the other nonprotein nitrogenous metabolites, but that these may even diminish, possibly through the conversion of amino-acids into urea. The muscle urea shows an increase when the blood urea rises above 150 mg per hundred cubic centimeters. In all cases showing increased muscle urea the absolute increase of urea in the blood was considerably less than in the musculature. The muscle creatinin increase was inconstant, and occurred only with severe creatinemia.

According to Rosenberg, then, normal muscle values for the rest nitrogen and urea are over ten times their concentration in the blood, and are not increased until the blood level rises above approximately two thirds of the normal muscle concentration. Retention of urea in the musculature occurs earlier than the other metabolites and its disproportionate increase in the muscles is probably due to the conversion of other nonprotein metabolites into urea.

Weiss and Vaughn²¹ recently reported a case of severe nephritis in which the blood urea twelve hours before death was 304 mg. and the nonprotein nitrogen 401 mg per hundred cubic centimeters. Post-

21 Weiss and Vaughn J Lab & Clin Med 7 229, 1921

mortem, the pericardial fluid contained 374 mg of urea nitrogen, the muscle 352 mg, and the liver 335 mg per hundred grams, respectively. Their technic is not given, but the results show a close approximation of the urea content of the blood, fluid and tissues. Andresen²² reports an equal distribution of urea, between the blood, organs and secretions, with the exception of tears and sweat, where a value three times that of the blood was found.

With the exception of Rosenberg, all of these investigators appear in fair agreement in regard to the uniform distribution of urea. He diverges considerably in regard to the urea value for normal musculature, but agrees with the others that the urea accounts for most of the nonprotein nitrogen retention in the body.

The distribution of ingested nitrogen was first studied by Soetbeer²³ in 1909. Four and one-half hours after a heavy meal of meat he found the total nitrogen in a dog's blood had increased 132 per cent, in the liver 41 per cent, and in the brain and muscles only 5 or 6 per cent. Seventy-two hours after nephrectomy, the total nitrogen in a dog's blood had increased 873 per cent, in the liver 144 per cent, in the brain 40 per cent, and in the muscles only 35 per cent. This would indicate a heaping up of the retained nitrogen in the blood before its accumulation in the tissues.

Von Monakow²⁴ showed that after a single ingestion of 20 gm urea per os in normal men, the blood urea rose in fifteen minutes and reached its peak in two hours, remaining slightly increased at twenty-four hours and returning to normal on the second day. If one day after the first ingestion, a second 20 gm was given, the blood urea level still returned to normal within two days. In other words, it was impossible to raise the blood level by repeated small doses of urea per os. Von Monakow assumes that most of the ingested urea passes into the tissues.

Lichtwitz²⁵ repeated these experiments, controlling them with simultaneous estimations of nitrogen elimination in the urine. After the ingestion of 20 gm urea per os, he found widely varying percentages of the retained urea in the blood. He concludes that the rest nitrogen is very unequally divided between the blood and other organs, and that it need not be increased in the blood, although the amount of nitrogen eliminated indicates a definite nitrogen retention.

Nonnenbruch²⁶ has recently repeated similar experiments on urea ingestion, retention and elimination. He finds that the variations in

22 Andresen *Biochem Ztschr* **116** 266, 1921

23 Soetbeer *Verhandl 26 Cong f inn Med*, 1909

24 Von Monakow *Deutsch Arch f klin Med* **115** 47, 224 1914, *ibid* **116** 1 1914

25 Lichtwitz *Klinische Chemie*, 1918

26 Nonnenbruch *Arch f exper Path u Pharmacol* **89** 200, 1921

blood urea nitrogen following the oral ingestion of 20 gm urea, do not parallel its elimination. For the most part the nonprotein nitrogen of the blood does not increase sufficiently to account for the urea ingested and falls much more rapidly than it is eliminated in the urine. In some cases, blood urea nitrogen was still increased after the ingested urea had all passed out through the kidneys. Several cases showed two peaks and two troughs in the blood rest nitrogen curves. On the basis of these findings, Nonnenbruch concludes that there is a marked difference of distribution between the blood and other tissues, that a normal blood rest nitrogen does not indicate the absence of nitrogen retention, nor, on the contrary, does an increased blood nitrogen indicate nitrogen retention in the tissues. He thinks that immediately after its ingestion urea is carried to the tissues and afterward returned to the kidneys for elimination.

SUMMARY

Although the studies with ingested urea indicate that during the period of its elimination there is no constant parallelism in the concentration of nitrogenous metabolites of the blood and tissues, both the estimation of the body fluid metabolites and the comparison of metabolites in the blood and tissues, strongly suggest a tendency to equilibrium throughout the organism. This does not necessarily mean that a normal concentration of metabolites in the tissues approximates that in the blood, but that the metabolites are distributed between them in a fairly constant proportion, and that an increase in one is paralleled by a proportionate increase in the other. No account, of course, is taken here of any but the simple metabolites, available sugar in the form of glycogen, or available rest nitrogen, urea nitrogen, creatinin or uric acid in more complex chemical forms, are incalculable factors. The distribution of creatinin and sugar throughout the body is for the most part unknown.

The distribution of metabolites between the blood and all the body fluids is fairly consistent. For clinical purposes, it appears justifiable to deduce from the concentration of metabolites in the blood, an approximately proportional concentration throughout the whole body. Nevertheless, until the distribution of metabolites for all the tissues is quantitatively determined, it will remain impossible to deduce accurately from the blood chemistry alone the degree of retention in the whole body.

CONCLUSIONS

- 1 In cases in which the blood metabolite level was not increased above normal, the concentration of sugar in serous effusions averaged 83.42 per cent of the sugar concentration in the blood. The urea nitrogen averaged 80.08 per cent, and the creatinin 67.28 per cent.

2 No characteristic difference in the metabolite concentration of exudates and transudates was observed

3 In cases in which the blood metabolite level was normal, the average concentration of sugar in the spinal fluid was 44.24 per cent of the blood sugar. Urea nitrogen averaged 58.15 per cent, and creatinin 68.3 per cent

4 Except for the absence of sugar in acute meningitis, no difference was present between normal and pathologic spinal fluids

5 In cases in which the blood metabolite level was increased, the metabolite concentration in the fluids varied *pari passu* with the changes in the blood

Thanks are due to Drs. S. Marx, White and George Fahr for their kind permission to study cases in the University Hospital, and to Dr. Henry L. Ulrich for the use of several private cases, and cases in the Minneapolis General Hospital

QUINIDIN IN AURICULAR FIBRILLATION

WITH SOME OBSERVATIONS ON ITS USE IN
COMBINATION WITH DIGITALIS *

T STUART HART

NEW YORK

One of the most spectacular medical discoveries of recent years is the effect which alkaloids of cinchona have on certain hearts presenting the phenomenon of auricular fibrillation

Quinin has been used for many years as a heart sedative, but its use specifically in auricular fibrillation dates from a report of two cases published in 1914 by Wenkebach ¹ in which its administration resulted in the restitution of sinus rhythm

As a result of his studies of the effect of various alkaloids of cinchona on patients suffering from auricular fibrillation, Frey ² came to the conclusion that quinidin was the least toxic and the most potent of these derivations, and because of its better solubility he advised the use of the sulphate instead of the pure alkaloid

Since Frey's paper in 1918 there have appeared in the literature the reports of more than 300 cases of auricular fibrillation treated with quinidin. In about one half of these its administration has been followed by a resumption of normal rhythm which has persisted for periods varying from a few hours to several months

We have as yet little accurate knowledge of the exact manner in which quinidin accomplishes its results, its optimum dose, the intervals at which it is best administered, its rate of elimination and its dangers. We know little of the type of case in which the normal rhythm is likely to be restored and the value of the resumption of control by the normal pacemaker is still open to discussion. The advantages and disadvantages of combining the administration of quinidin with other drugs has been studied but little.

It is only by accumulating considerable data that many of these questions can be solved, and it has, therefore, been considered worth while to place on record the clinical observations which we have secured up to the present time, notwithstanding their limited number and rather fragmentary character

* From the Medical Service of the Presbyterian Hospital

* Read before the Association of American Physicians, Washington, D. C., May 3, 1922

1 Wenkebach. Die unregelmässige Hertzthätigkeit und ihre klinische Bedeutung, Leipzig, 1914

2 Frey. Berl. klin. Wchnschr. 55 417, 451, 1918

This report is based on a rather careful study of fifteen persistent and two paroxysmal cases of auricular fibrillation. These were unselected cases such as one meets in the medical service of a large general hospital. The patients were observed carefully, were subjected to the usual routine physical and laboratory examinations of a well ordered medical service, and were studied by means of electrocardiographic records taken at frequent intervals.

The drug employed in all the studies has been the sulphate of quinidin, administered in capsules, each containing 0.2 gm. Our routine has been to give two preliminary doses of 0.2 gm. each allowing twenty-

TABLE 1—CASES IN WHICH THE ADMINISTRATION OF QUINIDIN WAS FOLLOWED BY SINUS RHYTHM

Case No	Sex	Age	Clinical Diagnosis	Duration of Fibrillation Before Quinidin	Quinidin, Gm	Duration of Sinus Rhythm
1	M	31	Chronic valvular disease, mitral stenosis, mitral insufficiency, cardiac insufficiency, repeated attacks of rheumatism	2 weeks	2.8 in 3 days 2.4 in 2 days	10 weeks 2 days
3	M	72	General arteriosclerosis, cardiac hypertrophy, hypertension, chronic nephritis	?	1.4 in 2 days	12 days
5	F	43	Hyperthyroidism, exophthalmic goiter, ligation of superior thyroid artery	3 years	1.4 in 2 days 1.8 in 2 days 3.6 in 4 days	24 hours 48 hours 0
9	F	68	Chronic nephritis, cardiac hypertrophy, hypertension	1 year	1.4 in 2 days 0.4 in 5 hrs	7 months 5 mos still continues
15	F	24	Chronic valvular disease, mitral stenosis, mitral insufficiency, cardiac hypertrophy, cardiac insufficiency, congenital syphilis	18 weeks	1.1 in 40 hrs 0.6 in 24 hrs 1.0 in 24 hrs	6 weeks 6 weeks ?
16	F	44	Exophthalmic goiter, ligation of superior thyroid artery, paroxysmal fibrillation	1 year	2.6 in 2 days 1.2 in 1 day 2.0 in 2 days	48 hours 72 hours 40 hours
17	M	68	Chronic myocarditis, cardiac insufficiency, paroxysmal fibrillation	5 years	0.4 daily for 12 months	1 year still continues

four hours for evidence of individual susceptibility to develop. After this, 0.4 gm. was given after eating three times a day over periods of variable length. As soon as a sinus rhythm had been reestablished the drug was immediately discontinued. Noteworthy departures from this routine will be mentioned in connection with the description of special cases.

Of the fifteen patients showing persistent auricular fibrillation, five recovered a normal rhythm after the administration of quinidin, in all fibrillation recurred after a longer or shorter period (Table 3), in four of these quinidin was given again and in each instance the normal pacemaker assumed control of the rhythm. One of these patients still

maintains a normal rhythm after an interval of five months, in the other three cases, a third period of quinidin was effective in one and ineffective in the remaining two cases

Flutter, as a transitional mechanism preceding a sinus rhythm, was recorded in two cases. In three other cases the administration of quinidin was followed by flutter (one case) and impure flutter (two cases) but in these cases the sinus never regained its control as a pacemaker.

In both paroxysmal cases, sinus rhythm promptly followed small doses of quinidin. In Case 16 of our series the periods of sinus rhythm were so brief and so similar to those of the control period during which no quinidin was given that our observations appeared to be of little or no value. The results obtained in Case 17 were more striking and will be referred to later in more detail.

In our experience, if quinidin was effective in producing sinus rhythm, this occurred within a few hours, or, at least, not longer than sixty hours after beginning the use of the drug. In one case sinus rhythm was restored in five hours after the administration of 0.4 gm. To none of the cases in which it was effective was more than 3 gm. given. In the cases which did not resume a normal rhythm, quinidin, 1.2 gm. a day, was continued from one to three weeks, but the prolonged administration seemed to have little or no effect. One patient (Case 1) who on two occasions responded to small doses of quinidin and in a third period failed to respond, was given, in a fourth period, 0.6 gm. daily for forty consecutive days with no apparent change in his rhythm or condition.

SELECTION OF CASES

We are able to add very little new information as to the type of case that is likely to be affected favorably by quinidin. In Table 1 are grouped the cases in which the administration of quinidin was followed by a sinus rhythm, in Table 2 the cases in which fibrillation persisted. A comparison of the sexes, ages and length of duration of fibrillation in these cases affords no explanation of the type of case in which quinidin exerts its peculiar influence. Nor does the clinical diagnosis help in solving this question. Cases of chronic valvular disease, mitral disease, general arteriosclerosis, chronic nephritis, chronic myocarditis, hyperthyroidism and hypertension can be found in both groups.

There is one feature, however, to which we would like to call attention which may possibly be of value in selecting the cases in which the administration of quinidin may be followed by the restoration of sinus rhythm. In reviewing our electrocardiographic curves, we have been impressed by the fact that those patients who in their control curves (i. e. those taken in the period before quinidin was given)

showed relatively large auricular waves or in which the coarse waves predominated over the fine waves, were more likely to regain a normal rhythm than those patients whose control curves showed only fine auricular oscillations

Of the control curves of fifteen cases of persistent fibrillation, nine presented very coarse waves or a mixture of fine and coarse waves in which the latter predominated. Of these, four reverted to normal rhythm. Six of these cases showed only the finer auricular waves and of these only one returned to a sinus pacemaker. A number of patients showing only fine oscillations had received digitalis over considerable periods, and this is an important point to be considered as will be seen when we discuss the influence of digitalis. In this con-

TABLE 2—CASES IN WHICH THE ADMINISTRATION OF QUINIDIN WAS NOT FOLLOWED BY SINUS RHYTHM

Case No	Sex	Age	Clinical Diagnosis	Duration of Fibrillation Before Quinidin
2	M	61	Multiple serositis, chronic myocarditis	5 years
4	F	30	Exophthalmic goiter, acute rheumatic fever, cardiac hypertrophy	7 weeks
6	F	37	Chronic valvular disease, mitral stenosis and insufficiency, rheumatic cardiac insufficiency	2 weeks
7	F	42	Chronic valvular disease, mitral stenosis, aortic insufficiency, cardiac hypertrophy, cardiac insufficiency	Over 2 years
8	M	60	Chronic myocarditis, cardiac hypertrophy, cardiac insufficiency	9 years
10	F	60	Chronic valvular disease, mitral stenosis and insufficiency, general arteriosclerosis, cardiac hypertrophy, cardiac insufficiency	Unknown
11	F	18	Chronic valvular disease, mitral stenosis and insufficiency, aortic stenosis, cardiac hypertrophy, cardiac insufficiency, rheumatic	7 days
12	M	61	General arteriosclerosis, chronic myocarditis, cardiac insufficiency	Unknown
13	F	42	Chronic valvular disease, mitral stenosis and insufficiency, cardiac hypertrophy, rheumatic, general arteriosclerosis	Unknown
14	F	16	Chronic valvular disease, mitral insufficiency, cardiac hypertrophy, adherent pericardium, cardiac insufficiency	7 months

nection, it is of interest to recall that cases of auricular flutter, in which auricular waves are, as a rule, relatively large, are more likely to recover a sinus rhythm spontaneously than cases of auricular fibrillation

QUINIDIN IN COMBINATION WITH DIGITALIS

A number of those reporting³ the effects of the administration of quinidin have pointed out that it may be associated with disagreeable symptoms and dangerous or even fatal results. Sir James Mackenzie

³ Lyster and Fahr. Arch Int Med 29:59 (Jan) 1922. Hewlett and Sweeney. J A M A 77:1793 (Dec 3) 1921. Mackenzie, J. Brit M J 2:576 1921. Orr, J. Brit M J 2:576, 1921. Benjamin and von Kapf. Deutsch med Wchnschr 42:10, 1921.

has particularly emphasized the possibility that the sudden coordinated contraction of the auricles may tend to dislodge emboli from intra-auricular thrombi

Levy has noted the not infrequent occurrence of ventricular tachycardia, and suggests that a persistent use of quinidin in such cases might lead to ventricular fibrillation with its obvious hazard

It is not surprising that the administration of a drug so dramatic in its effects should at times be attended with dangers, and in the present state of our knowledge it should be used only with great caution and under the closest supervision. None of our patients at any time presented alarming symptoms. A few had ringing in the ears, headache, nausea, vomiting, palpitation and increase in heart rate but these were very temporary and usually disappeared a short time after the drug was discontinued

In two instances which did not ultimately return to a sinus rhythm numerous ventricular extrasystoles were observed, but these were never so frequent as to suggest the approach of a ventricular tachycardia. One patient after recovering a sinus rhythm exhibited occasional auricular premature contractions

It was our impression that the greatest discomfort of which our patients complained was due to the palpitation and tachycardia. At the beginning of our work, in order to simplify our experiment as much as possible, we gave quinidin only to those patients who had never received digitalis or we withheld it for two or three weeks until we were sure that the heart was free from recent digitalis influences. This, of course, was the cause of much tachycardia and consequent discomfort. It was thought therefore, that it might be of some practical clinical value to compare in individual cases the result of the administration of quinidin alone with the result in subjects who had also been thoroughly digitalized

The results of our observations have been collected in Table 3. The cases are presented in the order in which they were studied, the "periods" represent successive intervals in which patients were observed, the time intervening between the periods varying greatly. For example Case 1 (rheumatic mitral disease) was first under observation in the hospital for about six weeks. The patient was discharged after sinus rhythm had persisted for four weeks. Six weeks later he began to fibrillate, and on his second admission to the hospital he was found to have been digitalized thoroughly. Without waiting for digitalis effects to wear off, he was given quinidin, which was promptly followed by a change to sinus rhythm which, however, lasted only two days. Quinidin was again administered but this time without interrupting fibrillation. In contrast, Case 5, a subject of hyperthyroidism with a metabolism rate of 56 above the normal, received quinidin in successive

periods separated by intervals of only two or three days. The first and second periods resulted in a resumption of control by the normal pacemaker, after this quinidin failed in abolishing fibrillation.

The use of alkaloids of cinchona in combination with digitalis has been opposed on the ground that their pharmacologic activities are antagonistic. Stokvis,⁴ experimenting on the frog's heart found that a combination of quinin and digitalis destroyed the depressing action of quinin and modified the excitation due to digitalis. Pezzi and Clerc⁵ state that in dogs to which quinin had been given, the subsequent administration of large doses of digitalin produced no toxic symptoms.

Schott⁶ has pointed out that in experimental animals quinidin, like digitalis, may produce heart block.

TABLE 3—QUINIDIN AND DIGITALIS

Case No	First Period			Second Period			Third Period		
	Drugs	Effect	Duration	Drugs	Effect	Duration	Drugs	Effect	Duration
1	Q	Sinus	10 wks	Q + D	Sinus	2 days	Q + D	0	
2	Q	0		Q + D	V slowing				
3	Q	Sinus	12 days						
4	Q	A slowing		Q + D	V slowing				
5	Q	Sinus	24 hrs	Q	A faster	48 hrs	Q	0	
6	Q	A slowing		D	V slowing				
7	Q	A slowing		D	V slowing				
8	Q	0		Q + D	A faster				
9	D + Q	Sinus	7 mos	Q	V slowing	5 mos + [*]			
10	Q	A slowing			Sinus				
11	Q	A slowing		Q + D	V slowing				
12	D + Q	V slowing							
13	D + Q	A slowing							
14	D + Q	A slowing							
15	D + Q	Sinus	6 wks	D + Q	Sinus	6 wks	D + Q	Sinus	?
16*	D + Q	Sinus	48 hrs	D + Q	Sinus	3 days	D + Q	Sinus	40 hrs
17*	Q	Sinus	1 year						

* Prolonged auricular fibrillation.

A = auricular, V = ventricular. Q = quinidin, D = digitalis.

Frey was opposed to the simultaneous use of quinidin and digitalis. Hewlett and Sweeney³ think that the administration of digitalis may have lessened the chances of the recovery of sinus rhythm in two of their cases.

In several papers⁷ published the latter part of 1921, Lewis and his associates Drury and Iliesco, pointed out that quinidin caused an "invariable and conspicuous reduction in the auricular rate." They obtained this evidence by applying special electrodes to the chest wall.

4 Stokvis. *Leçons de Pharmacologie* 3 41, 1905.

5 Pezzi and Clerc. *Presse med* 28 334, 1920.

6 Schott. *Deutsch Arch f klin Med* 124 208, 1920.

7 Lewis, Drury and Iliesco. *Brit M J* 2 514, 1921. Drury and Iliesco. *Brit M J* 2 512, 1921. Lewis, Drury, Iliesco and Wedd. *Heart* 9 55, 1921.

and were thus able to secure more clearly defined auricular waves in the electrocardiograms than when electrodes were applied to the extremities

Since these papers were published, we have scrutinized all our electrocardiographic records taken by the usual leads from the extremities. In these the auricular waves are often not prominent enough to make actual measurements of rate, but where these could be made, the administration of quinidin was uniformly found to slow the auricles and make the auricular waves more prominent.

Our curves further show that when digitalis was given, the auricular waves usually became smaller and more rapid, when it was withdrawn, these waves became coarser.

On several occasions we were able to watch in the same patient the effect of the administration of quinidin alone and later the combined effect of quinidin and digitalis. Curves illustrating the effect on the auricular activity are shown in Figures 1 and 2. The effect of giving quinidin in a case of auricular fibrillation without other medication was to make the auricular waves coarser. After a considerable period of quinidin, digitalis was added and its effect was shown not only by a slowing of the ventricular rate but also by a finer and more rapid auricular activity. Subsequently, quinidin was stopped and digitalis continued alone when its unopposed action was made evident by a further ventricular slowing and still smaller auricular waves. This would appear to be further evidence that there is an antagonism between quinidin and digitalis.

In Case 1 a delayed conduction and in Case 3 a partial block was observed during sinus rhythm, in neither instance could the effect be ascribed to digitalis. Case 15 also showed a delay in the conduction period but this patient was under the influence of both digitalis and quinidin.

As far as evidence based on success or failure in securing sinus rhythm goes, we have no definite proof that quinidin and digitalis are antagonistic.

An analysis of the fifteen cases of persistent fibrillation recorded in Table 3 shows that ten received in the first period quinidin only. In three of these, sinus rhythm was promptly secured. There were seven failures. Five patients received in the first period both digitalis and quinidin. Of these, two recovered a normal rhythm.

While the patients listed in Table 3 as receiving in the "first period" quinidin only were those who had taken no digitalis for two or three weeks preceding the period of observation and so were presumably free from its influence, it seems to us important to take into consideration the fact that a number of them had been digitalized more or less completely on earlier occasions. It was not possible to obtain sufficiently

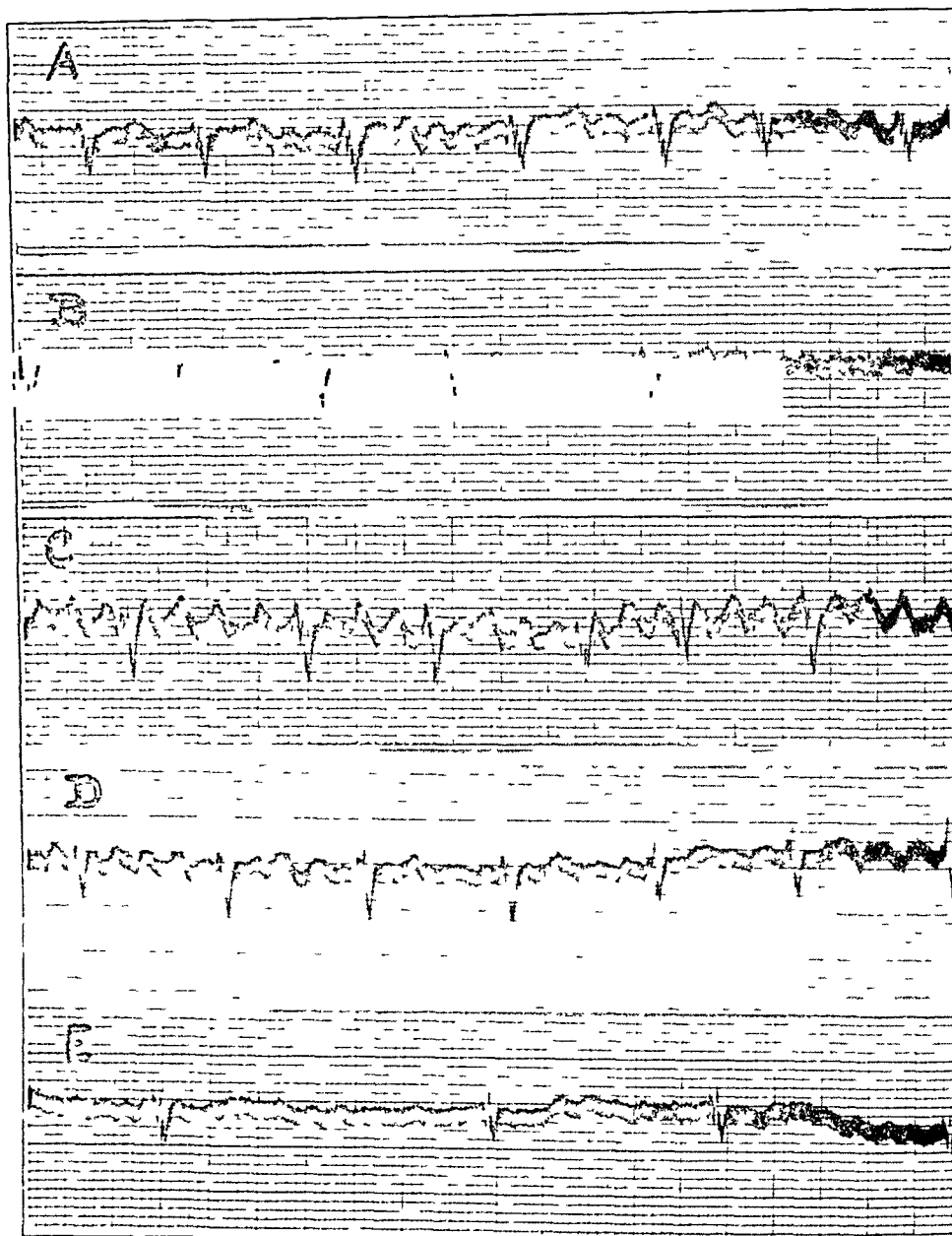


Fig 1—Case 4 Lead III A April 5 Fibrillation, ff waves rather coarse No drugs B April 18 Fibrillation, ff waves fine Digitalis only C May 24 Flutter, after quinidin, 0.2 gm No digitalis for three weeks D June 2 Fibrillation, ff waves medium size Taking quinidin and digitalis E June 13 Fibrillation, ff waves very small Digitalis only

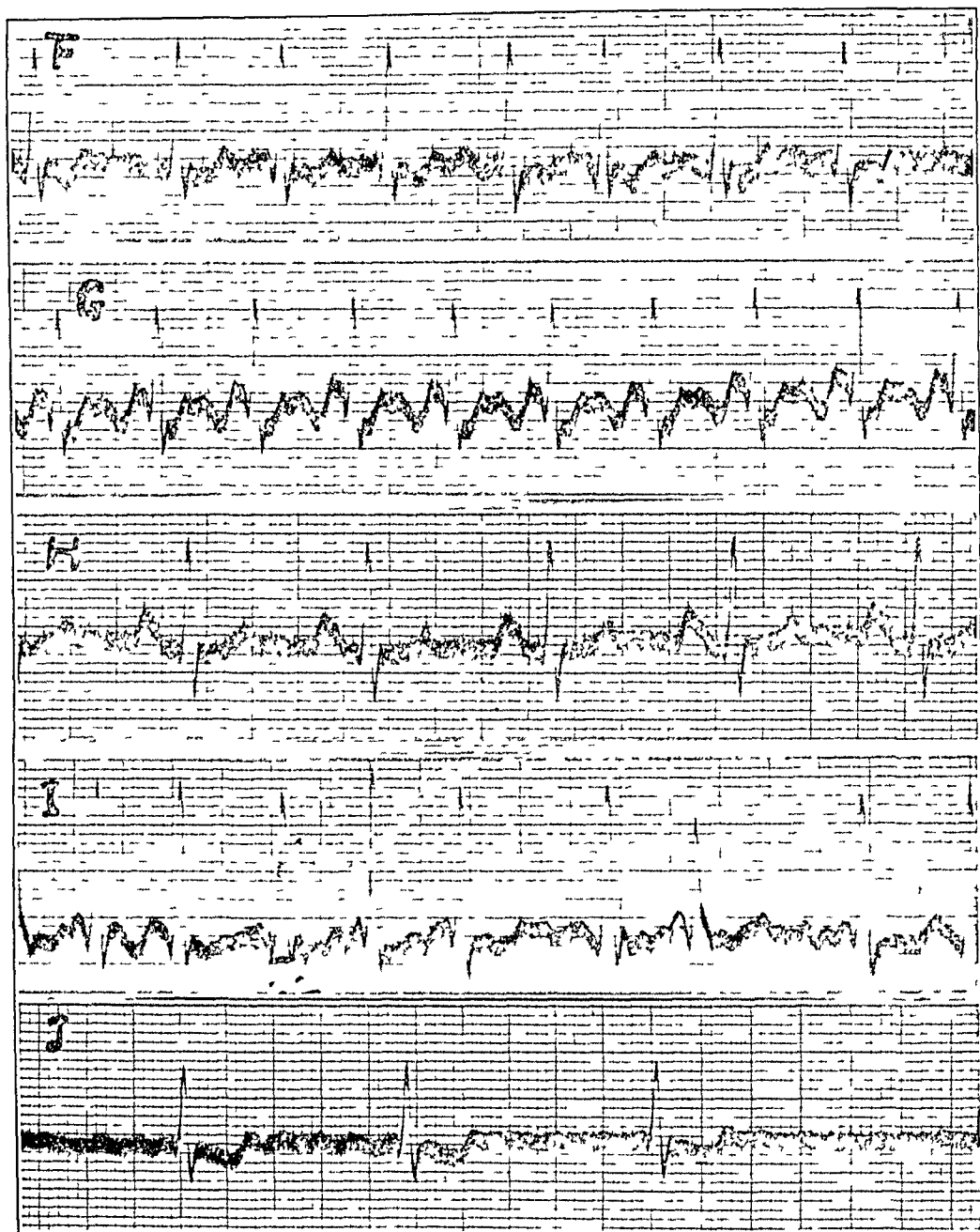


Fig 2—Case 1 Lead II F May 11 Fibrillation No drugs G May 14 Flutter after quinidin, 24 gm H May 15 Sinus rhythm after quinidin, 28 gm I July 28 Fibrillation No drugs for ten weeks J September 15 Fibrillation Full digitalization, ff waves very small

reliable statements as regards this feature from many of these patients, hence we have not recorded our incomplete data on this point. The effect of digitalis in diminishing the size of the auricular waves, and the experimental evidence that it can produce fibrillation, suggest that digitalis may have an influence in fixing a condition of fibrillation, and that a heart once digitalized may even after a very long period resist a return to sinus rhythm even though the more obvious influences of digitalis have disappeared.

A brief discussion of the comparative effect in individual cases of the administration of quinidin alone and of quinidin combined with digitalis affords some points of interest.

We may dismiss all those cases (Table 2) in which a sinus rhythm was not secured by stating that, in general, the effect of quinidin was to slow the auricular rate and accelerate the ventricular rate, while digitalis neutralized these effects, increasing the auricular rate and slowing the ventricular rate.

In several of the cases (Table 3) no comparative tests were made. Case 5 responded to quinidin on two occasions and failed to respond in the third. Case 15 was receiving digitalis through the whole period of observation. On three occasions the patient was given quinidin and this was followed by sinus rhythm each time. She has disappeared and we have been unable to report subsequent events. In this instance it does not appear that the digitalis seriously opposed the action of the quinidin, yet it is quite possible that without digitalis her periods of sinus rhythm might have been longer.

Case 1 responded promptly to quinidin, the normal pacemaker remained in control for ten weeks. During this period the patient had returned to his home, and when he again began to fibrillate, he was digitalized under the advice of his family physician. At this time he returned to the hospital and was admitted for observation, the administration of quinidin was again promptly followed by sinus rhythm which, however, lasted only forty-eight hours, quinidin was immediately repeated but a sinus rhythm was not secured. It is difficult to say that this was due to the digitalis, but it is suggestive.

Case 9 presents a number of features of interest.

The patient is a woman, aged 68 who has been under constant supervision for more than ten years. She is suffering from chronic nephritis, and for the past five years her systolic blood pressure has ranged from 200 to 230 mm Hg, diastolic pressure, from 120 to 140 mm Hg. Her heart is enlarged, and the mitral valve is incompetent. Except for occasional extrasystoles, her heart was regular until January, 1920. At that time she developed auricular fibrillation which terminated in twenty-four hours. Following this she had paroxysms of fibrillation, each lasting from one to three days, at four or five weeks intervals, until May, when the fibrillation became continuous. She was then digitalized effectively and the heart rate was kept between 70 and 80. In May, 1921, after having fibrillated persistently for one year and while still thoroughly under the influence of digitalis she was given, in the course of two

days, 14 gm quinidin. This was promptly followed by sinus rhythm and all medication was at once discontinued. A sinus rhythm was maintained for seven months until Dec 9, 1921, when she notified me about 2 a m that her heart was again irregular. She was seen a few hours later and the heart was found to be fibrillating with a ventricular rate of 140. Quinidin, two doses of 0.2 gm each, was given and the normal pacemaker resumed control five hours later. The ventricular rate was 86. The sinus rhythm has continued up to the present time.

In this instance the quinidin was equally effective both when the patient was completely digitalized and when she was taking no digitalis, but it may be noted that a smaller dose of quinidin was effective under the latter condition. At no time has this patient shown signs of cardiac insufficiency, except of a most insignificant degree, but her experiences of relief when the tumultuous action of the heart was replaced by an orderly rhythm left no doubt as to the marked increase in mental peace and subjective comfort induced thereby.

Such clinical evidence as we are able to present fails to demonstrate just how much influence digitalis exerts in opposing the action of quinidin, but, in the main, it accords with the experimental work in animals which indicates an antagonistic action of the two drugs.

PAROXYSMAL FIBRILLATION

Case 17 was of interest in this group.

A man, aged 68, has been under observation for more than four years. Without discoverable cause he has had paroxysmal attacks of fibrillation since 1916. His heart shows a very moderate enlargement and a slight systolic murmur at the apex and occasional extrasystoles when the sinus is in control of the rhythm. The roentgen ray shows an aorta measuring 7 cm. Between the paroxysms he has no signs of cardiac insufficiency, but when the heart fibrillates, he becomes excessively nervous, passes urine of low specific gravity at frequent intervals, and becomes dyspneic on any attempt at exertion. At first the attacks lasted only a few hours and occurred at irregular intervals separated by periods of several months. They had gradually increased in frequency and persisted for a longer time. In June, 1921, his attacks recurred at intervals of a few days and persisted for periods varying from nine to twenty-eight hours. June 23 he was seen a few hours after the onset of a paroxysm and it was decided to try the effect of quinidin. After his second dose of 0.4 gm he went to sleep and awoke at midnight with a regular heart. He was advised that if his attacks recurred he should take a dose of quinidin at once and if the irregularity continued the drug was to be repeated in two hours.

He was seen next August 16 and gave the following account from carefully written notes:

Date	Attacks Began	Quinidin, Gm	Note	Duration of Fibrillation
June 23	2 00 p m	0.4 (6 00 p m) 0.4 (9 00 p m)	Awoke at 12 Attack had stopped	10 hours (?)
July 5	8 30 p m	0.4 (8 45 p m) 0.4 (11 30 p m)	Awoke at 1 30 Attack had stopped	5 hours (?)
July 16	2 30 p m	0.4 (2 45 p m) 0.4 (5 30 p m)	Regular at 7 30 p m	5 hours
July 18	4 00 p m	0.4 (4 00 p m)	Regular at 6 00 p m	2 hours
Aug 10	8 30 p m	0.4 (8 30 p m)	Regular at 9 30 p m	1 hour

Since it appeared that quinidin had an influence in shortening the attacks, he was directed to take a daily dose (0.4 gm) as a prophylactic measure and to report the results in two weeks. He was not heard from again until he presented himself in January, 1922. Soon after his visit of August 16 he decided to go to France and he remained there until January, 1922. He reported that he had had no attacks and that he has taken one dose of quinidin each day throughout the whole period. He was advised to discontinue the quinidin but felt so confident of the beneficial effects of the drug and so fearful of a return of his paroxysms that up to the present time (May, 1922) he has, on one pretext or another, put off the day on which this advice is to become effective. He has had no attacks since Aug. 10, 1921. His heart is doing its work efficiently and there are no evidences of cardiac insufficiency.*

This experience suggests that quinidin may, in some instances, be taken over very long periods with no ill effects, and that it may act as a prophylactic measure to ward off these attacks which may be of a most distressing nature.

EFFECT OF THE RESTITUTION OF SINUS RHYTHM

Quite aside from the possible dangers involved in converting a condition of fibrillation into one of sinus rhythm, the question arises as to whether the patient is or is not benefited by substituting a sinus pacemaker for the impulses arising in a defective auricle. A priori, one would say that the resumption of the normal rhythm should be of advantage, and this we believe is true. In those cases in which cardiac insufficiency has been outspoken, the improvement in the general circulation following the return to control of the normal pacemaker, has not been better or worse, more rapid or slower than similar cases treated efficiently with digitalis. In this connection it may be recalled that the efficiency of the heart depends almost wholly on the integrity of the ventricular muscle, and if a reasonably slow rate can be secured, it makes very little difference whether the agent is an effective sinus pacemaker or digitalis. However, there is no question that the patient is far more comfortable when the delirious heart activity has been abolished. Patients are quite conscious of the change and dread the recurrence of the sensations produced by the fibrillating heart. I believe the mental attitude consequent on the disappearance of palpitation is a valuable asset. If sinus rhythm persists for any considerable time there is the additional advantage of discontinuing the administration of drugs for long periods.

* NOTE.—Seen Aug. 1, 1922. No attacks up to this time. Has taken dose of quinidin daily.

SUMMARY

1 Quinidin administered in fifteen cases of auricular fibrillation was followed by sinus rhythm ten times in five cases. In two paroxysmal cases it was followed by sinus rhythm in both instances.

2 Cases exhibiting electrocardiograms with coarse auricular waves appear to be affected more readily by quinidin.

3 There is some experimental and clinical evidence that the action of quinidin and digitalis are antagonistic.

4 Quinidin decreases the auricular rate and augments the ventricular rate. Digitalis increases the auricular rate and slows the ventricular rate.

5 A case of paroxysmal auricular fibrillation is reported in which under the daily administration of quinidin no paroxysms have occurred for nine months.

6 The advantages of the sinus rhythm over that of fibrillation are discussed.

UNUSUAL PAUCITY OF SYMPTOMS IN SOME CASES OF PONTOCEREBELLAR TUMORS DIAGNOSTIC DIFFICULTIES †

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Neoplasms developing in the pontocerebellar angle are presumably accompanied by manifestations referable to the cerebellum, pons and certain cranial nerves. If the tumor originates in the cerebellum, cerebellar symptoms will appear first. If the tumor originates in the eighth nerve the most frequently involved among the cranial nerves, vestibular or auditory symptoms will appear first. Besides the eighth, also the seventh, sixth and fifth nerves are affected quite frequently.

In any given case, in which a pontocerebellar involvement is suggestive, a systematic investigation with regard to the encroachment on the above mentioned portions of the central nervous system is usually made and a diagnosis is arrived at without great difficulty. In some cases, however, the situation is not so easy and only a repeated examination may render assistance. A third group of cases may be so baffling for want of gross or slight symptoms that no opinion can be rendered even after several examinations. In this category of instances the manifestations are so slight or so indefinite that not only the cerebellum or the cerebellopontine area but even an intracranial condition may not be thought of. Fortunately, such cases are rare, but, nevertheless, they do occur. The seven cases described herewith are examples of such an occurrence.

Before giving a description of them, attention is called to the detailed description of symptoms, for which each case was examined.

A carefully carried out examination was made in a systematic manner in each case.

1. The condition of the cerebellum and of its peduncles was determined from the following investigation: (a) The gait with regard to staggering toward one or the other side, (b) ataxia of the upper or lower extremities with regard to the finger-to-nose test, to overaction to dysmetria or hypermetria, (c) coordination of movements of the lower extremities in the test of placing the heel of one foot on various parts of the other limb, (d) diadochokinesia (quick pronation and supination), (e) the position of the head with regard to its inclination to one or the other side, also if an abnormal position found whether it is constant or permanent, (f) the presence or absence of

* Read at the meeting of the American Neurological Association held in Washington D C May 2-4 1922

abnormal voluntary or passive movements by resistance test According to Holmes and Steward, in a unilateral involvement of the cerebellum while the patient is flexing his arm on the affected side and the examiner opposes this flexion with his hand and then suddenly removes the latter, the movement of the flexion continues and the hand strikes the chest violently In normal conditions, the arm will continue for a moment flexing at first but will immediately stop and move in the opposite direction In passive movements, André-Thomas called attention to the following phenomenon in cerebellar diseases When the arm is raised to a horizontal position and the forearm is given repeated abrupt movements, the arm, on the side of the cerebellar lesion will show very little resistance The movements of flexion followed by movements of return (extension) are both of greater amplitude than on the normal side where resistance is greater and movements are slower Similarly, when both elbows are held and alternately adducted and abducted, the resistance is less marked on the affected than on the sound side In the lower extremities, if the thighs are placed at a right angle to the pelvis and the legs are extended but immediately released, the leg on the affected side will show less resistance and its return to the hanging position will be more rapid than that of its fellow on the sound side The same author observed that when the patient is told to raise his arm (on the affected side) and to let it fall on his head, it will do so like an inert body, namely, it will rebound several times (springlike phenomenon)

(g) Special reflex phenomena When the patient is placed on an elevated seat with his legs hanging, without touching the floor, and the test is made for the patellar tendon reflex, the normal knee jerk will consist of a sudden extension of the leg and slow return to the position of rest On the diseased side, if the reflex is present, the movement of extension is of a somewhat greater amplitude and is followed by a series of flexion and extension movements (pendulous type) The same form of reflex is observed in the biceps and triceps for the upper extremity in unilateral cerebellar lesions (A Thomas)

2 Compression of the pons itself in cerebellopontine angle conditions is ascertained from the presence or absence of symptoms referable to the motor and sensory pathways which pass through the pons Paresis or paralysis, anesthesia or analgesias or else paresthesias, changes of reflexes—all will be observed The latter, particularly, are frequent The knee jerks may be increased on the opposite side and not infrequently diminished on side of the lesion The toe phenomenon and ankle clonus may be present on the side of the plus knee jerk

3 The cranial nerves must be investigated with particular care As the eighth, seventh, sixth and fifth nerves are most frequently involved, the following symptoms will be observed, anesthesia of the

face on the side of the lesion (fifth nerve), facial palsy of the peripheral type with all the characteristic symptoms (seventh nerve), paralysis of the external rectus muscle on the affected side (sixth nerve), unilateral impairment of hearing, also vertigo with a tendency to fall to the affected side (eighth nerve)

4 The vestibular test by the Barány method has proven to be of considerable assistance in making a diagnosis of a pontocerebellar tumor, although in some cases it was shown to be unsatisfactory

In the presence of such an array of symptoms, the diagnostic problem of pontocerebellar symptoms appears to be solved with great facility. If not all the abnormal manifestations are present at the same time, at least some of them will be found after a careful search. But this is not always the case. Exceptionally, one meets with unusual instances in which the described multitude of symptoms are not all present, and if only one or two symptoms of the very many are observed, one's thoughts may find themselves totally diverted from the idea of pontocerebellar condition. Seven such examples verified by necropsies are submitted. A minute examination along the plan described was made in each case. The results are as follows

CASE 1—Tumor involving right cerebellar hemisphere, extending forward into the cerebellopontine angle on the same side but not displacing or disfiguring the pontine region very much

History—Patient was first seen eight weeks before the operation and nine weeks before death. He complained of headache which, however, was not of an unusually severe character. His gait and station were normal, there was no trace of leaning to one side in walking. The knee jerks were equal and intact. The plantar reflex was flexor in type by several methods. The patient complained of occasional blurred vision but the eye grounds were normal. The eye muscles functionated normally. There was no history of syphilis and the blood Wassermann was negative. The diagnosis was exceedingly difficult in view of total absence of gross objective phenomena. The headache, it is true, was persistent, but it was present only about two months, and the patient continued his occupation of a truck driver until about one month before the operation.

Examination—Repeated examinations were made. It was soon observed that while he was conversing or looking forward his head was slightly tilted toward the right side. During the subsequent days, and later on definitely, the head remained in the inclined position. Moreover, any attempt to incline it to the opposite side provoked some dizziness. He himself observed this when, accidentally, he would turn the head abruptly to the left side. The position of the head was such that the chin became directed toward the opposite shoulder. The patient soon commenced to complain of stiffness in the neck and careful interrogation revealed that this muscular stiffness was distinct on the right side but exceedingly slight on the left.

Diagnosis—The persistent headache and the persistent unilaterality of the head position together with muscular discomfort on the same side gave an indication of the possibility of an intracranial neoplasm situated presumably on the right side and in the cerebellar area. This presumption became stronger when the symptom of the pointing reaction made its appearance. It was at first equal and normal on both sides. It is only during the later examinations that an error, at first slight and later distinct, was observed. The error con-

sisted of an outward pointing with the right hand. This position was invariably uniform at each of the examinations. The vestibular test by Bárány's method was negative.

Course—Very soon the patient commenced to complain of frequent attacks of blindness lasting only a minute. The view of a right cerebellar involvement became stronger and stronger. The motor and sensory apparatuses remained intact throughout the entire period of observation. The eye grounds then showed no distinct pathologic lesions, but the veins commenced to appear to be somewhat dilated. A decompressive operation was advised and accepted. A mass was found as described above.

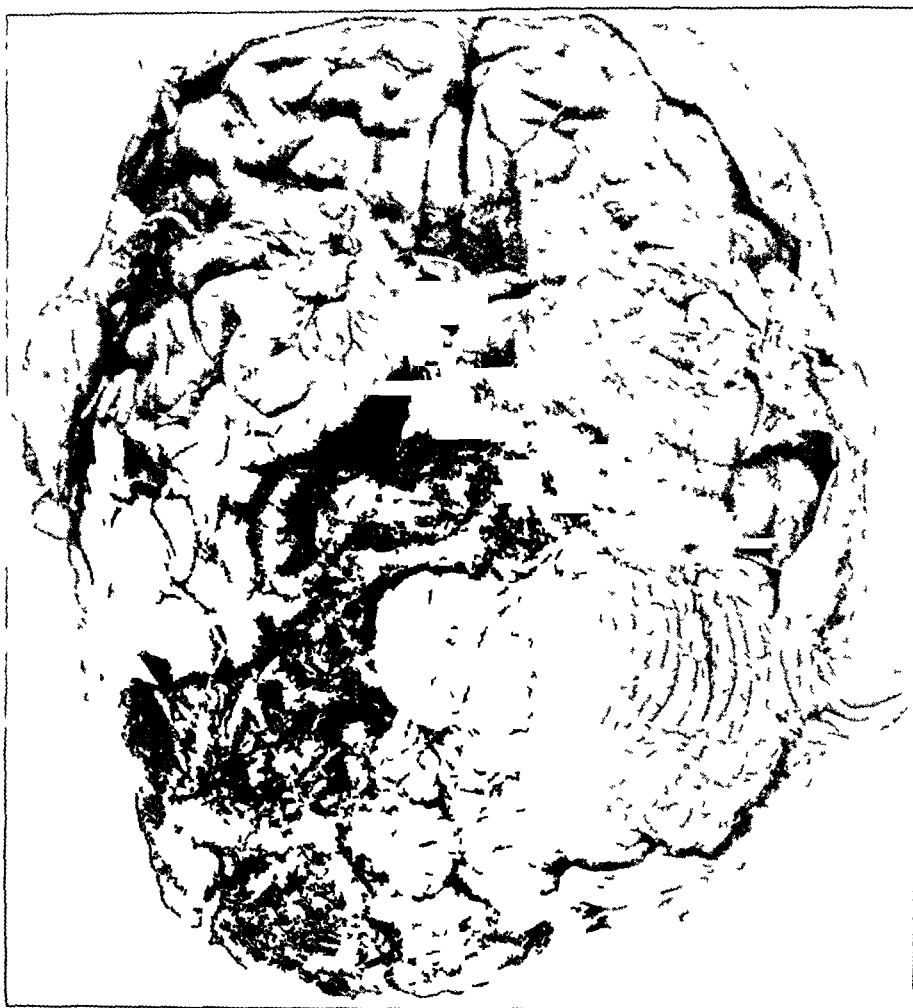


Fig 1—Tumor involving the right cerebellar hemisphere and extending forward into the cerebellopontine angle (Case 1)

CASE 2—Tumor situated in the right cerebellopontine area and producing no evident displacement of the pons with its structures. The mass encroached slightly on the fifth nerve.

History—The patient, aged 46, bookkeeper, during the last two years of his life, suffered from pain in the right side of his face. The pain was not continuous, but would occur under the influence of some emotion or else with the change of temperature. The facial area involved corresponded to the distribution of the first two branches of the trigeminus. Objectively, there was a hyperesthesia of the entire right side of the face and particularly with regard to the test for cold. The pain was not of a neuralgic character, and not

occurring in paroxysms. The patient described it as a burning pain at one time as a pulling pain at another. It was of a sharp character but of a steady and deeply seated aching. For many months the facial pain was the only morbid manifestation. There were no changes in the motor apparatus. Station, gait, reflexes, were all normal.

Examination—The patient was repeatedly examined and carefully gone over. Three months before he died, for the first time there was noticed an error in the pointing reaction on the right side. His finger invariably would deviate outwardly. It became more pronounced as the disease progressed. At the same time a dysmetria made its appearance on the right side in the finger-to-nose



Fig 2—Section of tumor from Case 1

test and remained unaltered until the end. One month before the termination the right knee jerk became diminished and remained as such. At no time did the eyes show any changes intraocularly or extraocularly. The vestibular test was negative.

Diagnosis—The diagnosis had to be based exclusively on the persistent right sided facial pain, abnormal right past pointing, right sided dysmetria of the hand and diminished right knee jerk. For a long time, however, the few latter symptoms were not yet in evidence, and a diagnosis of a right pontocerebellar condition in view only of facial pain on the right side could not logically be entertained.

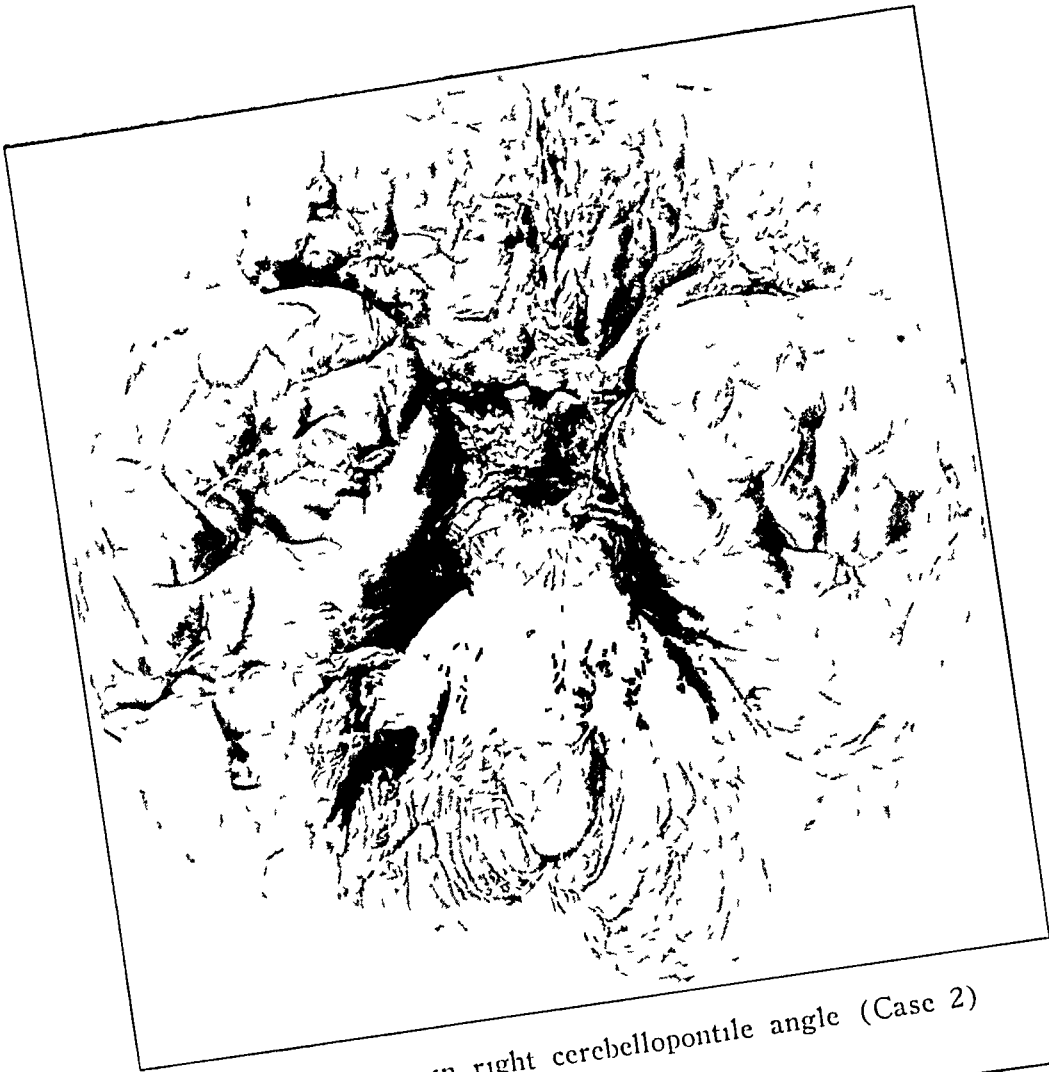


Fig 3—Tumor in right cerebellopontile angle (Case 2)

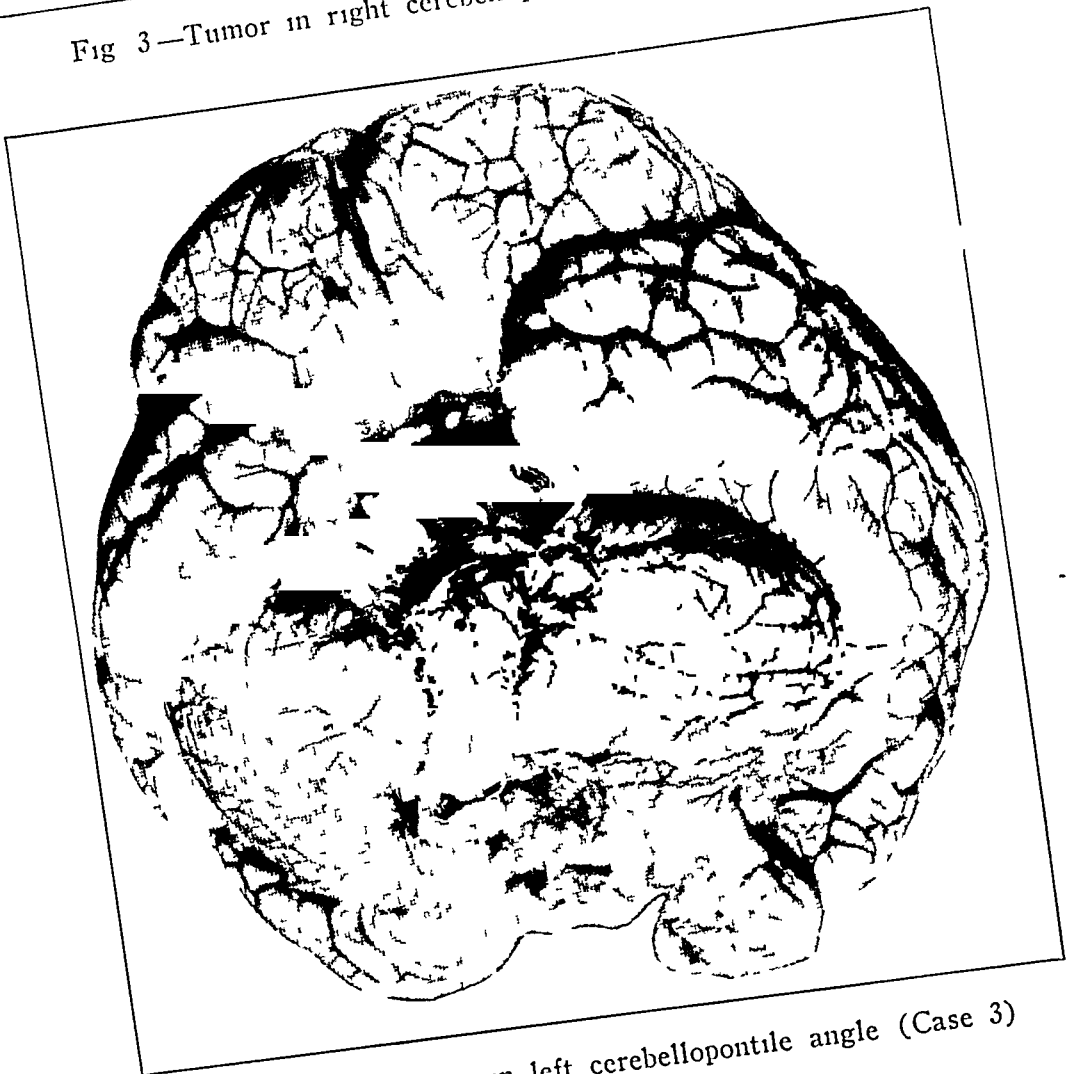


Fig 4—Small tumor in left cerebellopontile angle (Case 3)

Course—The patient died from a virulent attack of pneumonia

CASE 3—A small tumor in the left cerebellopontine angle

History—The patient, female, aged 17, complained of occasional vomiting and headache during the past year. These symptoms would occur at the time of her menstrual periods. A relationship between the two phenomena as cause and effect was considered by several physicians who were called in for an opinion and advice. The patient was given intensive opotherapy for many months without relief. Two months before her death it was noticed that the left side of her face was slightly deviated toward the right side. This facial



Fig 5—Large cystic mass in right cerebellar hemisphere pressing forward against the pons (Case 4)

paresis presented all the characteristics of peripheral involvement of the seventh nerve

Examination—A careful examination revealed no abnormal manifestations in the motor or sensory apparatuses and no involvement of cranial nerves, except the seventh. It was observed, however, that the pointing reaction of the left arm was invariably inward. Many examinations were performed and the inward pointing on the left side was persistent while the pointing with the right hand was always correct. A vestibular test was negative.

Diagnosis—In spite of the absence of gross symptoms, the past pointing together with the left facial paresis and the headache which became then more

persistent and continuous led to the thought of a left cerebellopontine pressure. No other symptoms were present during the last period of the patient's life.

Course—A decompressive operation was performed, but the patient died three days later.

CASE 4—A large cystic mass in the right cerebellar hemisphere pressing slightly forward against the pons.

History—Patient, male, aged 40, complained of dizziness and a slight headache in the low occipital region for six months, also of a stiffness in the neck.



Fig 6—Large neoplasm in right pontocerebellar angle (Case 5)

Examination—On examination it was noticed that his head was slightly tilted to the right and on attempts to turn it toward the left side he would become dizzy. The dizziness would last about one minute. The motor and sensory apparatuses, as well as the special senses, were all normal.

This condition lasted two months without alteration. Soon a new symptom made its appearance—the patient complained of occasional diplopia. The eye grounds as well as the ocular muscles remained intact. On repeated examinations an error of pointing reaction was observed in the right arm, namely inward and downward. A vestibular test was negative.

Diagnosis—The headache (though not severe) in the suboccipital region, cervical discomfort, dizziness, slight tilt of the head to the right and faulty pointing reaction—were the only symptoms for a diagnosis. Since these phenomena were uniformly persistent, a tentative diagnosis of a right cerebello-pontine lesion was made.

Course—The patient met with an accident falling down a flight of stairs and fractured his left thigh. On the third day he developed a violent type of pneumonia and he died on the fifth day.

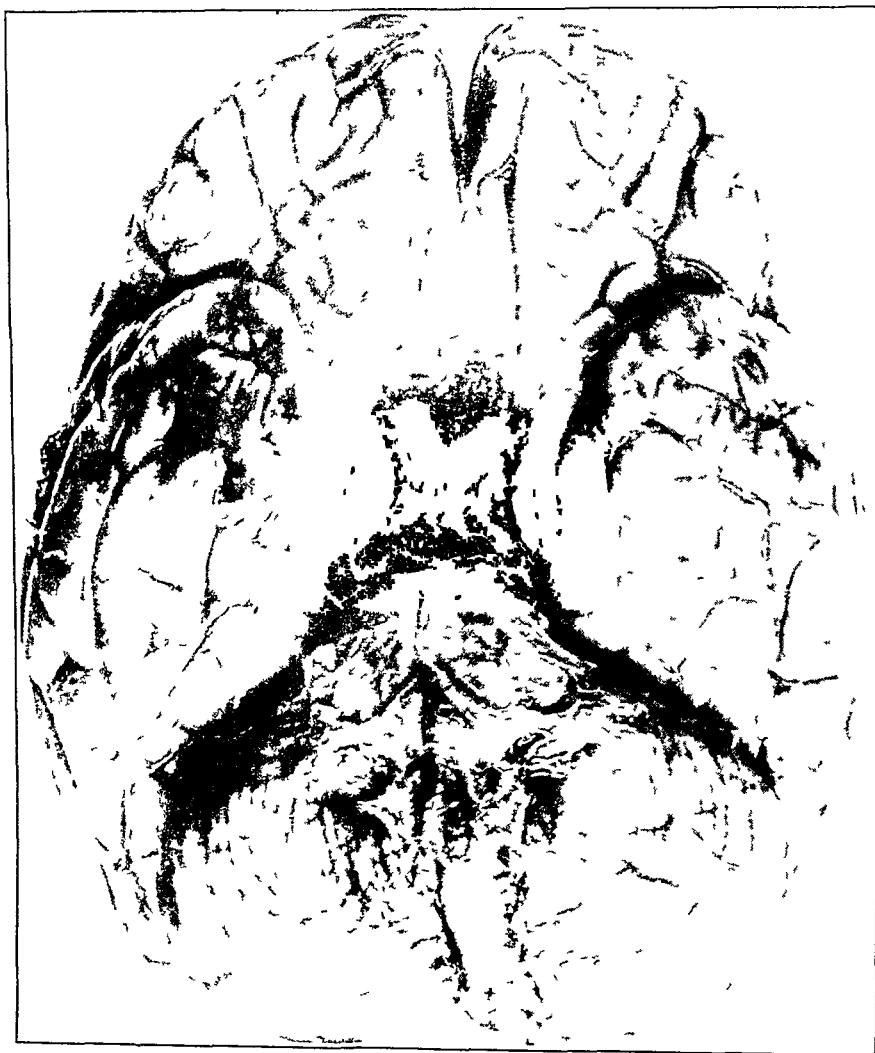


Fig 7—Small tumor in anterior portion of right cerebellar hemisphere lying close to the pons anteriorly (Case 6)

CASE 5—A large neoplasm in the right pontocerebellar angle pushing the pons to the left.

History—Man, aged 38, teacher of languages, complained for several years of attacks of vomiting, followed by severe headache which would last twenty-four hours. At first they occurred once in two or three months, but within the last year of his life, approximately once in two weeks.

Examination—On examination made six months before he died a slight engorgement of the retinal veins in the right eye with two hemorrhagic spots

in the left eye were noticed. The motor and sensory apparatuses were intact with the exception of a mild but a distinct hyperesthesia over the right side of the face. No other symptom was in evidence until two months before death. He then showed defective pointing reaction in the right hand with outward direction.

Diagnosis—The diagnosis was quite difficult at first in view of the facial hyperesthesia being virtually the sole objective symptom. Nevertheless, the



Fig 8—A mass lying in the anterior portion of the left cerebellar hemisphere close to the pons and adherent to the eighth nerve

persistence of it, together with the history of headache and vomiting (although only paroxysmal) gradually led one to suspect an intracranial condition. The appearance of the pointing reaction, which remained persistently confined to the right side, fortified me in my suspicion.

Course—A month later hemorrhages appeared in the right fundus oculi, and the patient complained of losing his eyesight. A right suboccipital decompression was performed but the patient died on the following day.

CASE 6—A small tumor of the size of a walnut in the anterior portion of the right hemisphere lying close to the medulla laterally and the pons anteriorly

History—Patient, woman, aged 48, gave a history of prolonged headache of a very mild character occurring once a month during a period of six years which was diagnosed as migraine. When I saw her, about six months before death, she presented a slight palsy of the external rectus muscle on the right side, disturbances of smell in the right nostril and some discomfort in the neck on both sides, which she qualified as a pulling sensation. The reflexes, sensations, gait, station were all normal. She complained of dimness of vision but the eye grounds were normal. This condition remained unchanged for four months when error in the pointing reaction of the right hand was noted; its reaction was outward and downward. This error persisted until the time of death. During the last three weeks a tilting of the head to the right was noticed and remained unaltered until the end. An operation was declined.

Course—Patient contracted a profuse diarrhea with a bloody discharge and died suddenly. She was found dead in bed.

CASE 7—A mass lying in the anterior portion of the left cerebellar hemisphere close to the pons and adherent to the eighth nerve. During the removal of the brain the affected hemisphere was much lacerated.

History—Patient, male, aged 45, a bartender by trade, complained during the last two years of his life of headache and occasional vomiting and occasional diplopia. He came under my observation two months before death.

Examination—He presented a tilting of the head to the left with the chin turned to the right. When the head was turned to the opposite side, dizziness would appear but it would last but a few seconds. With the exception of a markedly diminished left patellar tendon reflex there were no other evidences of an intracranial involvement. A vestibular test at that time was negative. Soon the pointing reaction became defective; its direction was inward and downward.

Diagnosis—The clinical picture was merely suggestive of a cerebellar condition.

Course—One month before the operation the patient suddenly became blind in his right eye. An examination revealed a marked venous engorgement with a few hemorrhagic spots in the right ocular fundus but no changes were seen in the left eye. A Barany test at this phase was positive and indicated the existing of a pontocerebellar lesion. A decompression was made in the suboccipital region, but the patient expired a few hours later.

DISCUSSION

An analysis of these cases demonstrates one striking fact, that while during many months no diagnosis could be made, the symptoms suggesting a pathologic condition approximately in the cerebellar vicinity commenced to make their appearance very late, so that early surgical interference could not be thought of. As to the symptoms themselves, their number was too small to permit strong inferences at first, but it is only because of their unilaterality and gradual and progressive development one after another, finally their persistence, after once having been established, that a tentative conclusion was reached as to their localization. It is not less remarkable that in five of the seven cases the increased intracranial pressure failed to produce changes in the ocular fundi. In the two positive cases, the changes appeared only a short time before death (two months and one month,

respectively) Retinal hemorrhages, with venous engorgement, were the symptoms observed. In view of their late development, the early diagnosis remained in suspense. Then entrance into the picture of the disease at once rendered the tentative localization already made more and more suggestive.

The positive sign common to all the cases was the error in the pointing reaction. The latter seems, therefore, of great value, and the search for it should be made persistently and repeatedly since in each of the seven cases it was a late manifestation, its absence in the early period of the disease was noticeable.

A special position of the head was present in four of the seven cases. The head was inclined toward the side of the tumor and when attempt was made to move it to the opposite side, headache and dizziness appeared, a diagnostic symptom to which I directed attention several years ago and which I had opportunity to verify on many occasions¹. The special position of the head, which remained unaltered until death, contributed, to a great extent, to the formation of a diagnostic opinion which was so difficult in view of the extremely small number of symptoms.

In two cases there was a persistent discomfort in the neck muscles consisting of a stiffness or of a pulling sensation. Although such a phenomenon has been observed, and reported in the literature, nevertheless, its inconspicuousness in both cases did not permit of attaching any diagnostic importance to it.

In Case 2 one symptom aroused a strong suspicion with regard to an intracranial involvement, in spite of the absence of gross and definite manifestations. This was a persistent pain with an objective hyperesthesia confined to the area of distribution of the first two branches of the fifth nerve. The pain was not of a neuralgic character but was a deep seated and continuous aching, pulling, or burning. It was so unmistakably different from the classical neuralgia and so persistent and so discomforting to the patient that attention was unavoidably directed to the possibility of an intracranial involvement.

Nerve involvement is observed very frequently in cerebellopontine neoplasms. Indeed, one may say, it is a strong diagnostic and localizing symptom. Curiously enough, only in two cases of my series the seventh and sixth nerves, respectively, were affected, but in a mild degree and only toward the termination of the disease. A very long period of time elapsed before these two nerves showed any involvement at all, and no definite diagnosis could be made from the very few symptoms present.

The vestibular tests by Bárány's methods are usually of considerable assistance in pontocerebellar conditions. The negative results

1 J A M A 50 461 (Aug 8) 1908

observed in six cases of the series are certainly striking. In one case it proved to be confirmatory of its diagnostic value during the advanced period of the disease. It seems, therefore, that in cases in which there is a great paucity of symptoms, the vestibular test itself is negative, although its usefulness would have been particularly enhanced in such cases had it given positive results.

CONCLUSIONS

This study indicates the possibility of unusual difficulties being present in the diagnosis of pontile angle tumors, and, therefore, leads to a delay in operative procedures, which, after the diagnosis has been made possible, become useless and highly dangerous.

The vestibular reactions which ordinarily render considerable aid in the diagnosis of pontocerebellar tumors are evidently not invariably positive in every case. Their absence, singularly enough, coincides with the absence of many other important symptoms on which a neurologic examination is based. The present study demonstrates the fact that integrity of vestibular reactions does not exclude the possibility of a pontile angle tumor.

In cases in which the diagnostic difficulties are great, one or two slight manifestations may obstinately persist at repeated examinations, such symptoms, although slightly or very slightly developed, should be regarded with suspicion, and if they are persistently unilateral a pontocerebellar condition should be thought of. Furthermore, the cases under discussion show that among such apparently insignificant symptoms the pointing error is of great localizing value, as it was present in each case. Its value is parallel with that of gait disturbance which is manifested in walking or falling toward one side in unilateral cerebellar conditions, it is also parallel with diadokokinesia (quick pronation and supination) which is intimately related to the functioning of the homolateral cerebellar hemisphere. The pointing errors are to be regarded as the result of consequences of a disturbance in the regulation and in the coordination of voluntary movements, which are controlled by the cerebellum, directly or indirectly, the rôle of the latter as a coordination center, or as an organ receiving its reflex influence on coordination from elsewhere in the central nervous system, is still in dispute.

Persistent pain in the area of distribution of one or two branches of the trigeminus, pain which is not of the typical neuralgic character, but has the character of pulling, burning, boring, etc., seems to be a highly suggestive symptom in the conditions under discussion, as Case 2 has proven. Here, again, its persistence at repeated examinations, and, particularly, its extremely deep and character, should

lead to the possibility of a material pressure on the fifth nerve at the level of the pons. Its occurrence in Case 2 seems to be highly instructive for diagnostic purposes.

After a careful consideration of all these special phenomena, it appears that while it is true that a diagnosis is almost an impossibility in the presence of such an extremely small number of symptoms as seen in this series of seven cases, nevertheless, the analysis of the special symptoms with their particular characteristics even in the early phases of the disease is bound to arrest attention. In all such cases a cerebellopontile condition should always be thought of and early radical intervention be considered seriously. To reiterate a negative vestibular test is not to be relied on for diagnosis as it is not conclusive and this study has shown that integrity of vestibular reactions coincide frequently with paucity of other neurologic manifestations.

Special emphasis is laid on this important fact that a limited or very limited number of morbid manifestations may be present even in cases in which the tumor is of a large size, as the findings in these cases have proven it amply. The dimensions, therefore, of a neoplasm must not be taken into consideration in every case when the proper estimation of the few symptoms present is diagnostically figured out.

H. W. Stenvers recently called attention to a very interesting differential diagnostic point. He observed in several instances that roentgenograms show erosions of the mesial part of the petrous bone in pontile angle tumors. If this statement is correct, these findings are of great practical value and add an important diagnostic symptom, particularly in cases in which the number of symptoms is unusually small.²

² J. Nerv. & Ment. Dis. **55** 54 (Jan.) 1922

OSTEOMALACIA *

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Osteomalacia is a generalized softening of adult bones which were at one time quite calcified and hard. It occurs in adult man and in some animals and birds. In man several types are recognized.

1 A mild form is found in pregnant, puerperal and lactating women, which recurs with each pregnancy. The skeletal changes become worse with each attack, but tend toward a spontaneous recovery when the drain of pregnancy and lactation is removed. A very similar group of cases arises in famine districts, or when the variety of diet is limited. The avidity of the tissues for calcium and phosphorus in these forms of osteomalacia is, however, undisturbed, and when these elements are added to the dietary in usable form, the patient recovers.

2 A second or senile type occurs in old people, in which the bone softening is, as a rule, confined to spine and pelvis. It generally progresses rapidly for a time, then ends in recovery with marked residual deformity.

3 A severe form occurs in pregnant, puerperal and multiparous women, in boys, men and castrated women, which is steadily progressive and shows no tendency toward recovery, ending in a marasmic state.

In lower animals practically all cases examined were of this last type. It occurs equally in male and female, mammal and bird. Up to the present time there have been forty-nine cases among mammals and thirty-four among birds. Considering the many species of animals exhibited, the disease is rather sharply limited to a very few groups.

TABLE 1—CASES OF OSTEOMALACIA IN MAMMALS AND BIRDS

MAMMALS			
	Cases	Males	Females
Primates	26	19	7
Lemurs	4	0	4
Carnivora	6	4	2
Hyraces	1	0	1
Rodentia	5	3	2
Marsupialia	8	5	3
AVES			Cases
Columbae			12
Galli			9
Psittici			6
Passeres			2

This table shows that 50 per cent of all the mammals infected are primates, and in this order are limited almost exclusively to the Cebidae.

* From the Laboratory of the Philadelphia Zoological Society

Of the birds 40 per cent are doves (*Columbae*), 30 per cent are pheasants (*Gallī*), 12 per cent parrots (*Psittici*). In the first two groups the disease is very extensive, involving practically every bone in the body, and the lesions are much more severe than those found in any of the other groups of animals or birds. Many other animals exposed to exactly the same environmental condition show a real or apparent immunity. Necropsy findings are practically the same in birds and mammals.

In mammals, the long bones of the extremities are early and seriously involved. They yield under the weight of the adult body, twist and bend, causing extraordinary and grotesque deformities. Very soon the animal is unable to stand (cage paralysis).

In birds, the more serious lesions occur in the bones of the thorax, ribs and sternum. Claws and beak are frequently affected, often so softened that the bird is unable to pick up seeds.

The gross appearance of the bones is again roughly similar. The skull may be reduced to the consistency of writing paper, the margins of the bony plates are often markedly thinned, while centers show irregular spots of thinning interspersed with areas of thickening. In one case, an adult *Cebus*, the skull was so completely deprived of calcareous matter that it could be twisted. The ribs are irregularly softened. Thin translucent areas are found associated with white opaque fusiform or nodular beadings, especially at the costosternal junction and at the epiphyses. These beadings are apparently efforts at splinting, occurring where the weakness from excessive bone absorption is the greatest. The whole rib may be soft, the consistency of soft rubber, and almost entirely deprived of the bone salts. It will cut with scarcely any crunch and bend easily in the fingers.

The long bones show the same irregular thickening closely associated with areas so thinned that they are almost translucent. They are usually distorted because of the body weight, generally a forward bowing. Fractures are extremely common, often more than one is found at necropsy. These injuries may show no attempt whatever at repair, or more often a fibrous or inadequate cartilaginous union. In all instances the deposition of bone salts is very inefficient. More rarely there may be an overactive effort at repair, but here also with only a scanty deposition of bone salts. In the immediately adjacent areas there may be marked subperiosteal reaction, but, as a rule, the periosteum shows no reaction at all.

In man, the small joints often become deformed early and in appearance suggest an osteo-arthritis. Large joints may ankylose. The spine and pelvis are involved sooner or later, ending often with a total loss of power over the legs.

Besides the bone lesions, there is constantly present in these animals a more or less severe secondary anemia, a lowered alkalinity of the blood and a fermentative type of intestinal indigestion. All show slight dilatation of the stomach, with some atrophy of walls. The small intestines are thin walled, and the accumulation of gas gives to it a sausage appearance. Lactic acid was found once in the urine. The kidneys show mild nephritis changes, and in some, fatty degeneration or merely pallor is present.

Microscopically, the bones show in every case a more or less pronounced absorption of the calcareous salts (osteoporosis) and with the abnormal bone absorption there is a marked tendency toward the deposition of newly formed osteoid tissue in which calcification never reaches the normal. Sections show osteoid margins along each lamella of bone, covering in the parts still calcified. Normal lamellar arrangement of bone is sometimes retained, usually, however, the bone cortex is very thin with coarse, broad trabeculae, wide marrow spaces and only the slightest tendency toward the formation of Haversian systems. Lacunae and osteoblasts may be normal but contain little calcareous matter. Osteoblasts and osteoclasts may be few, equal in number, or the osteoclasts may be unduly numerous. Osteophytes and Sharpey's fibers, similar to those found in osteitis deformans, are frequently seen. Cancellated tissue is often much decreased, especially at the ends of the long bones. In some cases it has practically disappeared.

The periosteum may be sharply marked off from the bone cortex, as a rule, it shows no activity in its osteogenetic layer. The subperiosteal bone may be very thin, almost like paper, but normal in appearance. At the junction of the bone and the cartilaginous rib there is often a thickening, seemingly from the periosteum. Endochondral bone formation at the epiphysis is usually abnormal, as shown by its irregularity of foci and extremely large intratrabecular spaces, osteoblasts are numerous. The marrow cavity is wide and filled with red more or less edematous marrow. The bone marrow is very much like that found in aplastic anemias. It is generally scanty and collected near the ends of the bones. Bone shows active removal of old trabeculae by means of numerous osteoclasts, and the production of fibroblasts, some of which differentiate into bone cells for forming new trabeculae in which only scanty amounts of lime are deposited. Rarely ever is normal bony architecture reproduced.

An analysis of the bones shows a marked diminution in the amount of calcium and an excess of sulphur and magnesium. Metabolic studies show a loss of calcium primarily in the feces, but also a marked increase in the calcium output in urine, with the retention of sulphur and magnesium. A salt metabolism of one monkey was attempted on four four-day periods, which showed a high calcium and phosphorus loss with a moderate magnesium and sulphur retention.

No hypothesis yet advanced satisfactorily explains the observed facts. The one most generally accepted is Fehling's¹ theory, based on Foichner's observation that osteomalacic women were improved or cured by the removal of the ovaries. His idea was that the disease was due to a hyperfunction of the internal secretion of the ovaries, which produced a sympathetic paralysis of the vasomotor system, which, in turn, caused a hyperemia of the bones and a consequent abstraction of calcium. Careful examination of our autopsy material failed to reveal any specific or distinct lesion in the ovaries, or in any of the ductless glands. All were, however, apparently smaller than glands usually found, with the exception of the adrenals, which were either normal in size or larger, and in two cases much congested. Minor changes were noted in the thyroid in a few instances. Ovaries and testicles were grossly normal in appearance. Microscopically, spermatazoa were found to be much reduced in numbers.

The second theory of origin was that in some manner the alkalinity of the blood was decreased, which permitted the lime salts to go into solution. This decreased alkalinity might be due to (1) a primary ductless gland disorder, especially a dysfunction of those glands which in some manner were concerned with bone metabolism, (2) a loss of alkali, (3) an excessive acidity, either the result of a predominantly acid forming diet, or due to an excessive production of acid in the body. These factors might act independently or in coalition, and might act directly or indirectly through their influence on the ductless glands. The absorption and deposition of salts are dependent on the chemical equilibrium of the cells, and slight shiftings of the acid base equilibrium of the cells in either direction may be sufficient to cause extensive lesions.

In favor of this view are many observations and experiments. Virchow² described deposits of calcium in the organs of people dying of osteosarcoma, osteomalacia and other disease states in which there is excessive bone absorption. These deposits were found in all organs, but especially those excreting an acid into their cavities—lungs, stomach and kidneys. In these organs there was no evidence of diffuse necrobiosis previous to the deposit of the lime salts. It seems probable therefore, that the calcium was precipitated into the normal organ because the excretion of the acid in these parts left the tissue fluids relatively more alkaline and less able to hold the same amount of calcium in solution. Pawlow³ found a bone condition very similar

1 Fehling. Ueber Wesen und Behandlung der Osteomalazie, Arch f Gynaek **28** 1890, **29** 1891.

2 Virchow. Virchows Arch f path Anat **197** 112, 1909.

3 Pawlow, cited by Babkin. Ztschr f Stoffwechsel **11**:561, 1910.

to osteomalacia in dogs, in which a pancreatic fistula was continued for long periods. Here there was a constant loss of alkali through the fistulas, and the body alkalis had to be utilized for neutralization of the acid production.

Diet has at various times been proposed as a factor, at least, in the production of this condition. This idea has gained considerable weight through the increase of the number of cases recorded from famine districts and parts of Central Europe where the dietary is restricted and unbalanced. Voit⁴ fed pigeons for one year on diets very poor in calcium, with clinically no ill effects, but found at necropsy marked wasting of the sternum and skull.

In adults a poor calcium diet can be continued for long periods without any apparent ill effect, because the losses from the blood and soft tissues can be replaced from the bones. In the young, however, poor calcium diets very promptly cause weakness and flexibility of the bones.

During pregnancy the calcium requirements of the animal are markedly increased. Steenbock and Hart⁵ found that the production of milk made heavy drains on the skeleton, unless the amount of calcium and phosphorus contained in the food was abundant. Forbes and Beegle⁶ also noted that calcium was often lost when the animal was storing nitrogen. Steenbock⁷ and his associates have produced osteomalacia in cattle by feeding them "shorts," a diet high in magnesium but otherwise well balanced. Sherman and Gettler⁸ found, on a diet giving a high acid ash, as rice and potatoes, that 33 per cent of the acidity could be accounted for by increased ammonia production and about 40 per cent by the increased acidity of the urine, leaving a remainder which must be eliminated or neutralized by sodium or potassium carbonate of blood or other fixed alkali. Etienne⁹ found that excess of magnesium in an otherwise well balanced food apparently caused a continual loss of calcium. Schiff and Strausky injected subcutaneously a magnesium salt and produced a marked increase in calcium output in urine and a diminution in calcium retention. In children after weaning calcium disturbances are frequent and often are due to disorders of digestion and obscure irregularities of nutrition.

⁴ Voit, E. Significance of Calcium in Animal Nutrition, *Ztschr f Biol* **16** 55, 1880.

⁵ Steenbock and Hart. Influence of Function on the Lime Requirements of Animals, *J Biol Chem* **3** 23, 1913.

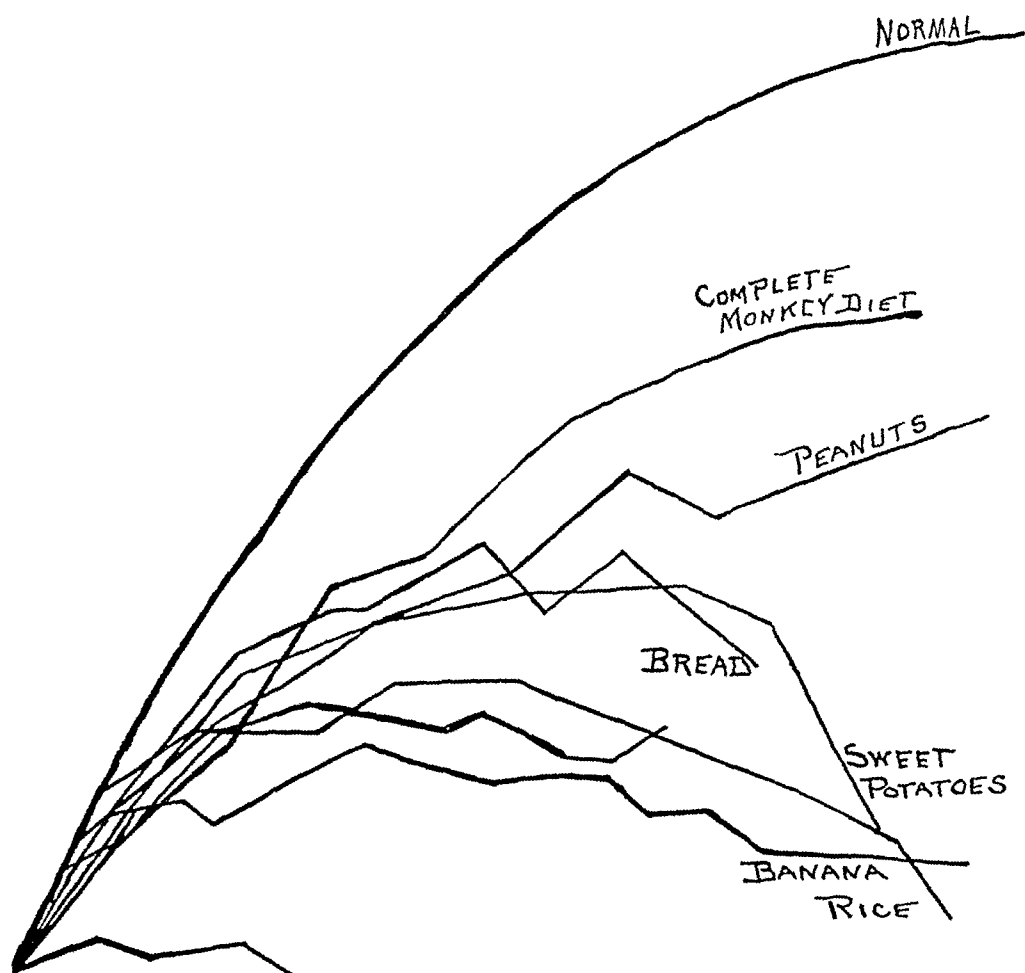
⁶ Forbes and Beegle. Mineral Metabolism of the Milch Cow, Ohio Agriculture Experiment Stat Bull 295.

⁷ Steenbock and Hart, Development of Osteoporosis by Swine Induced by High Magnesium Intake, *J Biol Chem* **3** 23, 1913.

⁸ Sherman and Gettler. The Balance of Acid Forming and Base Forming Elements in Foods and Its Relation to Ammonia Metabolism, *J Biol Chem* **11** 323 1912.

⁹ Etienne. *J Physiol et Path* **14** 108, 1912.

From these observations and experiments, it seemed advisable, first, to examine carefully the diet of the Cebidae monkeys, in which family the disease was most prevalent and most severe. The food of these monkeys, two bananas or two apples or six small sweet potatoes, with a portion of boiled rice about the size of an egg, occasionally bread, peanuts and lettuce. This diet was studied first, for the amount of essential protein, fat, carbohydrate and ash, then, for the general character of the protein and ash, and third, for the ability of this entire diet and of each of its constituents to maintain normal growth, health and



The average growth curves are plotted for the entire time on which the rats were fed the separate constituents of this diet and they are compared with the curve of normal rats on a well balanced diet and with rats on the complete diet fed to these monkeys.

reproduction. A diet is considered normal when it maintains a normal weight curve, gives a normal immunity to disease, allows completion of a normal span of life, and allows normal breeding of healthy young that shall be vigorous when weaned.

Analysis of this diet computed from Atwater's tables and by actual analysis of the amounts of food consumed by the animal in four four-day periods gave (1) Protein low in quantity and poor in quality,

especially low in phosphorus content (2) Fat very low (3) Carbohydrate very high, almost eleven times the value of all other ingredients (4) Ash decidedly low and predominantly acid Further analysis of this ash showed only a trace of calcium and phosphorus and iron, only a small amount of sodium and potassium, sulphur and magnesium were slightly higher (5) Vitamins A, B and C were present in extremely small amounts Vitamin A was exceptionally deficient and in the rations of some days was entirely lacking

The accompanying graph shows the effects of the separate constituents of this diet and the diets as a whole on the growth and nutritive balance of rats Rats were chosen for this study because they were susceptible, and the only animal for which we have normal standards for comparison Lettuce, corn and apples did not support life, bananas gave little growth with no reproduction, but life continued for a considerable length of time Eggs were extremely detrimental to the health of rats, causing diarrhea with many fatty acids in the stool, eczema and early death Sweet potatoes caused distention of the abdomen, sore eyes, diarrhea with frothy stools, rough coarse fur, hump back, no breeding and considerable atrophy of testicles Rice produced a loss of weight, constant diarrhea, hump back, swollen joints, sore eyes and no breeding With bread the general condition was good, weight curve depressed and diarrhea frequent Reproduction was much reduced The young died or were eaten by parents before weaning With peanuts the eyes were sore, a diarrhea frequent, but coat was fair and general condition good The rats bred poorly and the young all died before weaning In other words, not any constituent of the diet was able in itself to support life and health The entire diet gave a generally good condition, with a moderate depression of weight, immunity and breeding Frothy diarrhea was present in most of the rats at some time during the experiment, and in some was constant Litters were vigorous at birth but were always eaten by the parents

A second series of rats was subjected to the principal ingredients of this diet for one month and was then fed with additional food which, theoretically, should replenish the deficient diet and make it adequate, as shown by resumption of normal growth curve

Table 2 shows the additions necessary for corrections of the separate ingredients of the diet

The complete diet was rendered adequate by the addition of fresh, whole milk and leafy vegetables, or by butter fat, salt mixture and leafy vegetables

In this monkey diet several factors are of importance (1) Low vitamin content, especially vitamin A, factors which are essential for life and growth (2) A high carbohydrate diet which on oxidation

TABLE 2—CORRECTION OF DIET INGREDIENTS

DIET	CORRECTED BY
Rice	casein, salt mixture, carrots or lettuce, butter fat
Bread	casein, butter fat, salt mixture, especially phosphorus
Potato	salt mixture, especially sodium chlorid and calcium carbonate
Raw peanuts	salt mixture
Bananas	casein, yeast or carrots
Corn	casein, tryptophan, lactalbumen
Egg	detrimental to rats, no recovery
Apple	casein or gelatin, butter fat
Onion	casein or gelatin, butter fat

yields an acid ash and which favors the growth of intestinal bacteria producing acid and gas. The acid from these two sources must be neutralized either by the alkalis derived from food or from the body storage. This diet, however, is abnormally low in ash, and especially in the alkaline salts of the ash, therefore making it an ideal diet for the production of osteomalacia.

The full significance of predominantly acid forming diets has only lately been fully recognized, especially as they affect protein storage, and, therefore, growth and recuperation by deflecting the nitrogen and draining the body alkalies. Goto shows that in experimental acidosis the carbonates are first called on, next, the alkali phosphates, particularly the potassium phosphate of muscles and calcium carbonate of bones.

The main service of milk is probably due to its alkaline residue when oxidized in the body, and its plentiful supply of calcium, iron and vitamins.

This diet is deficient in those salts that were lacking in the bones of the monkey and which the animal was excreting in excess of its intake, possibly because of the excess of magnesium.

This ration at best would only keep the animal in calcium and phosphorus equilibrium, and any upset making even the slightest demand on its alkaline storage would be sufficient to set up a faulty metabolism.

CONCLUSIONS

It would seem that in this inefficient diet lies, if not the cause of osteomalacia, at least a very potent factor in its production.

1. The disturbance of the calcium and phosphorus metabolism may be due primarily to the deprivation of the alkaline salts from the diet (famine osteomalacia), or, second, to a drain from the alkaline storage of the body, associated with a deficient diet, as in the cases of osteomalacia of pregnancy and lactation, or, third, in the combined action of a diet faulty in more than its salt content, which, by the production of acid in its oxidation and by favoring the development of acid

forming bacteria, causes a drain of the body alkali for the neutralization of this acid, or, fourth, and this is more probable, especially in the severe form, it is due to the combination of all these factors acting upon the ductless glands and through them altering definitely the inorganic metabolism

2 In severe osteomalacia the power to retain and absorb calcium and phosphorus is practically lost, while in the cases developing during famine, and in pregnancy and lactation, this power is retained. These subjects immediately recover when calcium and phosphorus are presented in usable form. This permanent loss of power to absorb or retain calcium and phosphorus can be explained only by some definite changes in the endocrine balance.

3 It is important, also, that while this disease is very common among the Cebidae it has never been found among our Macaques. This may be due to the fact that owing to the storage sacs in the mouth of the Macaques more food proportional to body weight is consumed, and to a probable essential difference in the basal metabolism of these families and individuals. All the factors enumerated do tax the metabolic resources of the body and depress the functions of the endocrine glands. Detailed and accurate quantitative studies of normal metabolism and their effect on the ductless glands will alone give a more definite answer to the problem. The starting point of treatment must be a diet adequate in vitamins and containing a proper inorganic balance.

THE ALKALI RESERVE IN "ROENTGEN-RAY SICKNESS" *

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Ever since the introduction of roentgenotherapy in medicine, constitutional reactions following irradiation have been observed. These reactions are manifested clinically by symptoms which may appear any time after irradiation, from a few minutes to a day or more, usually from four to six hours, and which may run the gamut from slight headache and malaise, anorexia, nausea and vomiting to complete prostration, compelling the patient to remain in bed two or three days. Ordinarily, the symptoms subside in a few hours.

The exact cause of these manifestations is not known. Several theories as to their origin have been offered, the merits of which, with one exception, it is not the purpose here to discuss. Lange,¹ on the basis of the fact that the administration of sodium bicarbonate seemed to ameliorate or to prevent the onset of postirradiation symptoms, suggested that acidosis might be the cause. It is assumed that the term "acidosis" was used in the ordinary sense as meaning a lowered alkali reserve. This theory appeared to have some experimental substantiation in the work of Denis, Martin and Aldrich.² These workers showed that a large dose of roentgen rays, lethal when applied over the abdomen of rabbits, was not fatal when applied over the chest or legs with the abdomen protected, and that the blood of the former animals showed a lowered alkali reserve. They state, "The results suggest the hypothesis that acidosis may be a factor in 'treatment sickness' following abdominal irradiation." However, as they point out, the dose applied over the abdomen of these animals was large enough to be fatal, about five times the amount usually given any one portion of a patient's body, and, whereas clinical "treatment sickness" appears a few hours after irradiation, no objective symptoms appeared in the rabbits for several days. It should also be noted that the reduction in alkali reserve in these experiments did not occur for several days after irradiation and that the most marked lowering seemed to be a terminal affair.

* From the Department of Medicine, Harvard Medical School, and the Medical Service of the Peter Bent Brigham Hospital.

1 Lange, S. The Cause and Prevention of the Constitutional Symptoms Following Deep Roentgen Therapy, *Am J Roentgenol* 3 356, 1916.

2 Denis, W., Martin, C. L., and Aldrich, M. A Study of the Relative Toxic Effects Produced by Regional Radiation, *Am J M Sc* 160 555, 1920.

Following the intravenous injections of radium deposit in dogs, Theis and Bagg³ found that the nitrogen elimination was increased and that examination of the nitrogen partition showed that ammonia was increased proportionally more than urea, suggesting an acidosis. It is of interest that these dogs manifested symptoms very similar to those following heavy roentgenotherapy.

During the fall and winter of 1920-1921, numerous patients in the roentgen-ray treatment clinic of Dr. George W. Holmes at the Massachusetts General Hospital were advised to take sodium bicarbonate for the nausea following treatment. No definite benefit seemed to result. Similar observations were recorded by Pfahler⁴. In December, 1920, an opportunity presented itself to study the reaction of the blood of a patient undergoing irradiation. A man (J. J. M., W. S. 239,973, aged 28) with metastatic carcinoma of the peritoneum and mesentery of unknown origin (operative diagnosis), who had received frequent roentgen-ray treatments during the preceding seven months, was readmitted to the West Surgical Service of the Massachusetts General Hospital in order to keep him under observation while undergoing intensive roentgen therapy. This patient usually had nausea and vomiting after irradiation and was sometimes compelled to remain in bed during the reaction. Dec. 14, 1920, three days after a treatment over an abdominal area, venous blood was drawn into a test tube containing a crystal of potassium oxalate. The carbon dioxide combining power of the plasma was determined by Miss Margaret Woodwell in the laboratory of Dr. J. H. Means and found to be 78.5 volumes per cent. December 15 another abdominal area was irradiated. About three hours later, during the postirradiation nausea, venous blood was drawn in the same way and the carbon dioxide combining power of the plasma found to be 80 volumes per cent. About twenty-six or twenty-eight hours after the next treatment, the carbon dioxide dissociation curve of the blood of this patient was determined by Dr. J. H. Means and Dr. A. L. Barach, to whom I am greatly indebted for this data, and the hydrogen-ion concentration was found to be normal (pH 7.35). The carbon dioxide content of the arterial blood (whole blood) was 54.5 and that of the venous blood 60 volumes per cent. Another patient (F. C. W. S. 237,990, male, aged 32) with metastatic melanosa, who had received frequent heavy treatments over the abdomen for five months, showed a plasma carbon dioxide combining power of 80 volumes per cent, the blood being taken in oxalate one half hour after irradiation before nausea had begun.

³ Theis, R. C., and Bagg, H. J. Effect of Intravenous Injections of Active Deposit of Radium on Metabolism in the Dog, *J. Biol. Chem.* **51**: 525, 1920.

⁴ Pfahler, G. E. The Cause and Prevention of the Constitutional Effects Associated with the Massive Doses of Deep Roentgen Therapy, *Am. J. Roentgenol.* **5**: 5, 1918.

The results on these two patients indicated that there was no fall in the alkali reserve after irradiation. In fact, the figures for the plasma carbon dioxide combining power are unusually high, as both 75 and 80 volumes per cent have been recorded as the upper limits of normal. To secure more evidence, animal experiments were planned with the idea of determining whether or not relatively moderate doses of roentgen rays were followed by the clinical signs of "treatment sickness" and by a lowering of the alkali reserve of the blood. These experiments were carried out during the fall and winter of 1921-1922 at the Peter Bent Brigham Hospital. Further clinical observations were made as opportunities presented themselves.

The plasma carbon dioxide content of two dogs receiving weekly irradiations was studied over a period of about three months. Dog 1 was a black and white mongrel weighing 12 kilos. Dog 2 was of airedale extraction, not quite full grown, and weighing 10.3 kilos. Dog 3, a yellow mongrel weighing 11 kilos, was kept as a control under the same conditions as the other two dogs and received no radiation until this experiment was finished, as described below. The radiation was applied over the upper part of the abdomen for the first two or three times and then alternately over the back and over the upper abdomen, always involving the viscera of the upper two-thirds of the abdomen. The rays were produced by a broad focus Coolidge tube activated by an interrupterless Victor-Snook transformer, using a spark gap of 9 inches between spheres, a filter of 5 mm of aluminum and a target-skin distance of 8 inches. With this setting 50 milliamperes were at first given to both dogs. This quantity of radiation was sufficient to make Dog 1 vomit once or twice in two or three hours and to refuse food. Dog 2, on two trials with 50 ma. minutes and one with 60, gave no evidence of a reaction. However, 75 ma. minutes were sufficient, with one exception, to make him vomit once. The animals were bled from the external jugular vein at varying intervals after irradiation, the blood being collected under liquid petrolatum in a tube containing a crystal or two of potassium oxalate. It was then transferred to a centrifuge tube and centrifuged under oil. The carbon dioxide content of the plasma was determined by Van Slyke's method (1917).

The blood bicarbonate in dogs apparently has lower normal limits than in man. Hjort and Taylor⁵ found the plasma carbon dioxide combining power of apparently normal dogs to vary from 42.9 to 67.3 volumes per cent in twenty-four animals. The blood was not manipulated under oil and the plasma was equilibrated with air containing 5.5 per cent carbon dioxide. I found that the plasma of dog blood

⁵ Hjort, A. M., and Taylor, F. A. The Effect of Morphine on the Alkali Reserve of the Blood of Dogs Gassed with Fatal Concentrations of Chlorine, *J. Pharmacol. & Exper. Therap.* **13**: 497, 1919.

taken and centrifuged under oil gave off, on the average, from 7 to 8 volumes per cent more carbon dioxide after equilibration with my own alveolar air than before, i. e., the actual carbon dioxide content of dog plasma was from 7 to 8 volumes per cent less than the carbon dioxide combining power when equilibrated with presumably normal human alveolar air. In view of the reaction which takes place between plasma and corpuscles when carbon dioxide is lost from the blood, which results in a slight decrease in the amount of plasma bicarbonate, and in view of the subsequent equilibration with carbon dioxide at about the tension of human alveolar air, the method used by Hjort and Taylor undoubtedly gave figures slightly higher than the actual plasma carbon dioxide content. In several determinations of the plasma carbon dioxide content of two normal dogs, the blood being collected under oil, Gauss⁶ found one 43.8 volumes per cent and one, when the animal was excited, as low as 40.9 volumes per cent. Therefore, one could hardly say that the alkali reserve of dog blood was below normal limits unless the carbon dioxide content of plasma handled under oil went below 40 volumes per cent, which is probably a conservative estimate.

Two preliminary determinations of the carbon dioxide content of the plasma were made before any radiation was given. On Dog 1 the second of these and the first after irradiation was begun were not made with the animal fasting. Chanutin⁷ has shown that the ingestion of a quantity of meat raises the carbon dioxide combining power of dog plasma from 5 to 9 volumes per cent, the peak coming anywhere from one to four hours after the feeding. The remainder of the observations were made with the animals fasting, except for the last on Dog 1, just before he was etherized, as necropsy showed the stomach to be full of undigested meat. This final observation, nine days after the last irradiation, was the only one in which the alkali reserve was lowered definitely below the normal and was probably due to a terminal acidosis. The results are recorded in Tables 1 and 2. There was no evidence that irradiation lowered the alkali reserve, whether vomiting occurred or not. Table 3 gives the observations made at intervals on the plasma carbon dioxide content of Dog 3, the control animal.

To determine whether or not even a slight reduction in the alkali reserve occurred during the hours following irradiation, a supplementary experiment was run with Dog 3 as the subject. With the animal fasting, four control observations on the plasma carbon dioxide content were made at intervals on March 1, 1922, and one on the morning of March 2. As shown in Table 4, there was a slight fall which

⁶ Gauss, H. The Effect of Morphine on the Alkali Reserve of the Blood of Man and Certain Animals, *J. Pharmacol. & Exper. Therap.* **16** 475, 1920.

⁷ Chanutin, A. Animal Calorimetry—The Influence of the Ingestion of Meat and of Glycine and Alanine on the Carbon Dioxide Combining Power of Blood Plasma, *J. Biol. Chem.* **49** 485, 1921.

TABLE 1—OBSERVATIONS ON THE PLASMA CARBON DIOXID CONTENT OF DOG 1 AFTER IRRADIATION

Date	Quantity of Radia- tion*	Reaction	Bled After Irradiation, Hours	Plasma CO ₂ Content, Vol per Cent	Weight in Kilos
10/10/21	0			53.8	
10/13/21	0			61.9	12.0
10/17/21	50	Vomited	Not bled		
10/25/21	50	Vomited	18	65.6	
10/31/21	50	Vomited	6	47.8	
11/ 7/21	50	Vomited	3	52.5	
11/14/21	75	Vomited	3½	49.4	
11/21/21	75	Vomited	2	49.2	
11/28/21	75	Vomited	4	58.9	
12/ 5/21	75	Vomited	3	49.6	
12/12/21	75	None	2½	64.6	10.3
12/19/21	40	None	2½	67.9	
12/26/21	0			55.4	9.0
1/ 2/22	50	None	2	58.4	
1/ 9/22	40	None	3	49.5	7.5
1/18/22	0		Bled just before etherization	36.4†	6.4

* In milliamperes minutes with a target skin distance of 8 inches, a spark gap of 9 inches (between spheres) and a filter of 5 mm of aluminum. The radiation was applied either over the upper abdomen or over the back in such a way that the viscera of the upper two thirds of the abdomen were involved each time.

† Only at the last observation was the plasma carbon dioxide content reduced below the normal. As this was made nine days after the last irradiation when the animal was extremely weak, it was thought to be a terminal acidosis, not related directly to the irradiation.

TABLE 2—OBSERVATIONS ON THE PLASMA CARBON DIOXID CONTENT OF DOG 2 AFTER IRRADIATION

Date	Quantity of Radia- tion*	Reaction	Bled After Irradiation, Hours	Plasma CO ₂ Content, Vol per Cent †	Weight in Kilos
10/10/21	0			47.2	
10/14/21	0			48.3	10.3
10/17/21	50	None	Not bled		
10/25/21	50	None	16	50.2	
11/ 1/21	50	None	6	50.0	
11/ 8/21	60	None	3	47.3	
11/15/21	75	Vomited	2½	48.3	
11/22/21	75	Vomited	2	49.5	
11/29/21	75	Vomited	4	46.6	
12/ 6/21	75	None	Not bled		
12/13/21	60	None	3	52.0	9.8
12/20/21	0			47.3	
12/27/21	50	None	3	46.4	8.0
1/ 3/22	50	None	2½	57.1	
1/11/22	35	None	2	49.4	6.6

* In milliamperes minutes as described under Table 1.

† No reduction of the plasma carbon dioxide content below the normal was found.

TABLE 3—OBSERVATIONS ON THE PLASMA CARBON DIOXID CONTENT OF DOG 3*

Date	Plasma CO ₂ Content, Vol per Cent	Weight in Kilos
10/11/21	53.4	
10/17/21	44.8	11.0
12/16/21	52.0	11.7
12/23/21	51.6	
12/30/21	51.9	12.1
1/ 6/22	51.5	

* This animal was not irradiated during this period. He was kept as a control under the same conditions as the other two.

possibly was related to the fast. On the morning of March 8, the fasting animal was given an irradiation of 75 ma minutes with the setting described above. He was bled at intervals of approximately two hours during the day and once the following morning, the first bleeding being made about an hour and a quarter after irradiation when he was showing evidences of nausea. One and three-quarters, three and one-half and four and one-half hours after irradiation he vomited a colorless watery material containing no free hydrochloric acid. During this period he was noticeably inactive. About six hours after the treatment he became more lively and in a short time he appeared to be quite normal. The experiment was repeated April 3 with practically the same

TABLE 4—OBSERVATIONS ON THE PLASMA CARBON DIOXID CONTENT OF DOG 3
MADE AT INTERVALS AFTER IRRADIATION*

Date	Time of Bleeding	Plasma CO ₂ Content, Vol per Cent	Weight in Kilos	Remarks
3/1/22	9 50 a m	52.0	11.1	Animal fasting, no roentgen ray
	11 50 a m	48.3		
	2 15 p m	49.1		
	3 45 p m	48.3		
3/2/22	9 30 a m	46.2	10.5	Animal fasting, roentgen ray, 75 ma-min over abdomen ending 7 55 a m vomited watery material at 9 35, 11 30 and 12 30, vomitus contained no free HCl
3/8/22	9 15 a m	49.6		
	11 10 a m	56.4		
	1 20 p m	54.9		
	3 30 p m	50.8		
	5 05 p m	49.0		
3/9/22	9 15 a m	51.8	10.5	Animal fasting, roentgen ray, 75 ma-min, over abdomen ending 8 15 a m, vomited watery material at 9 30, 11 00 and 12 30, free HCl present in specimen at 9 30 a m
4/3/22	9 15 a m	53.5		
	11 10 a m	56.7		
	1 20 p m	56.5		
	3 05 p m	50.6		
4/4/22	5 05 p m	52.7		
	9 15 a m	52.5		

* The setting for the irradiation was as described under Table 1. The figures show a slight rise instead of a fall in the plasma carbon dioxide content during the first few hours after irradiation.

result, except that the first vomitus contained free hydrochloric acid. It will be seen in Table 4 that, on both occasions, the plasma carbon dioxide content, instead of diminishing during the reaction, rose slightly and then fell slightly below the first figure.

Aside from the question of the alkali reserve, it may be of interest to record other facts observed during the experiments. Epilation of hair with desquamation of the skin over the irradiated areas appeared about four weeks after the first application of the rays, but no definite erythema or destruction of the skin occurred. The first three or four irradiations seemed to cause the animals slight transient discomfort in spite of the vomiting. After that they began to show lack of energy and to refuse food for two or even three days. About the sixth week it became evident that both dogs were losing weight. From that time

on, as the weights recorded in the tables show, the loss was increasingly rapid. Dog 1 lost altogether 5.6 kilos, or 46 per cent, of his weight, and Dog 2 lost 3.7 kilos, or 37 per cent. During this period the control dog gained 1.1 kilos. The emaciation was so extreme and developed so rapidly during the last month of the experiment that it does not seem reasonable to attribute it alone to the periods when the dogs refused food, although this must have been a factor. During the last month of the experiment both animals frequently passed loose and at times watery stools, occasionally containing streaks or flecks of blood.

Although Dog 2, a young animal, reacted less than the older one, as far as vomiting was concerned, he showed more evidence of weakness and prolonged anorexia. He was found dead on the morning of Jan 15, 1922. Unfortunately, I was away from the laboratory and was not notified until two days later, the body being kept meanwhile in the refrigerator. At necropsy, nothing definitely abnormal was found except a perforation of the anterior wall of the stomach which was interpreted as a postmortem change. This interpretation was confirmed by the fact that no evidence of an inflammatory reaction in the margin of the perforation was found on histologic examination. No areas of ulceration or necrosis were seen in the intestinal tract.

Dog 1 vomited more consistently after irradiation but seemed to maintain his strength better and to recover his appetite sooner than the younger animal. January 18 his respirations were deep and slow, quite suggestive of the hyperpnea seen in clinical acidosis. As it did not appear likely that he would live more than a few hours, he was bled and then etherized and a necropsy was performed immediately. The plasma carbon dioxide content was 36.4 volumes per cent, undoubtedly indicating a diminished alkali reserve. In view of the fact that the dog had not been irradiated for nine days, this acidosis was thought to be a terminal thing and not related to "treatment sickness." At necropsy, this animal showed nothing definitely abnormal grossly aside from extreme emaciation. The stomach contained considerable undigested meat. The colon contained semifluid yellow feces which in the rectum were blood tinged. No hemorrhagic areas, ulceration or other evidence of destruction of epithelium were found anywhere in the gastrointestinal tract, as have been described in rabbits by Denis, Martin and Aldrich² and in dogs by Hall and Whipple⁸ and Warren and Whipple,⁹ following a single dose of roentgen rays large enough to kill the animal.

8 Hall, C. C., and Whipple, G. W. Roentgen Ray Intoxication, *Am J M Sc* **157** 453, 1919.

9 Warren, S. L., and Whipple, G. W. Roentgen Ray Intoxication. I. Unit Dose Over Thorax Negative—Over Abdomen Lethal. Epithelium of Small Intestine Sensitive to Roentgen Rays. II. A Study of the Sequence of Clinical, Anatomic and Histologic Changes following a Unit Dose of Roentgen Rays, *J Exper Med* **35** 187, 1922.

Dog 3, which had been given 75 ma minutes over the abdomen March 8 and April 3, was etherized and a necropsy performed April 4, thirty hours after the second irradiation and about twenty-four hours after he showed signs of recovery from the resulting reaction. The necropsy showed nothing abnormal in the gross.

Microscopic examination of the liver, pancreas, kidney, suprarenal and celiac ganglion of Dog 1 discloses nothing abnormal. No evidence of an endarteritis is seen in any of the sections. Of the parts of the gastro-intestinal tract, the stomach shows the most marked changes. There is a definite increase in the fibrous tissue of the stroma of the mucosa. In many places the gastric glands do not extend to the muscularis mucosae. The gastric tubules in some areas are replaced by fibrous tissue and in other places all that remains of a tubule is three or four of the deeply acid-staining parietal cells completely surrounded by what seems to be young fibrous tissue. Whatever the damaging mechanism may have been—the rays themselves directly or stimulation of fibrous tissue indirectly—the parietal cells seem to have been distinctly more resistant than the chief cells. The columnar epithelial cells of the surface and pits show no evidence of damage. The lymphoid cell content of the solitary nodules has been markedly reduced. In the small intestine the columnar epithelial cells appear normal. Cells of the lymphoid series are greatly diminished in number in the tips of the villi and in many instances are absent. The nodules of lymphoid tissue in the tunica propria show evidences of destruction, invasion by fibroblasts and endothelial cells and regeneration of germinal centers. The large intestine shows nothing definitely abnormal. A section of a mesenteric lymph node shows very rare lymphoid cells, except around the periphery, where new germinal centers have formed, the cells in which show many mitotic figures and from which lymphoid tissue is invading the node in chords. The reticular tissue is infiltrated with large numbers of polymorphonuclear leukocytes and endothelial cells. The latter are manifesting great phagocytic activity, some of them containing as many as four polymorphonuclear cells. The splenic nodules are reduced in number and size and there is a marked diminution in the number of lymphoid cells in the pulp of the spleen.

Because of postmortem changes, sections from the tissues of Dog 2 are unsatisfactory. However, they disclose nothing contradictory to the findings in the tissues of Dog 1.

Sections of the liver, pancreas, suprarenal, celiac ganglion, stomach and large intestine of Dog 3 show nothing definitely abnormal. In the villi of the small intestine the lymphoid cells are somewhat reduced in number. An abdominal lymph node shows changes similar to those seen in the node of Dog 1 but to a much less extent. The splenic nodules are small. In the center of some of them there is a reaction

consisting of clusters of large mononuclear cells with clear nuclei and pale staining cytoplasm, some of which are phagocytic. The splenic pulp contains large numbers of migrating leukocytes and a reduced number of lymphoid cells.

Observations on the plasma carbon dioxide combining power of two patients undergoing roentgen-ray treatment in the wards of the Peter Bent Brigham Hospital are recorded in Table 5. From 250 to 300 ma

TABLE 5—OBSERVATIONS ON THE PLASMA CARBON DIOXIDE COMBINING POWER OF TWO PATIENTS RECEIVING ROENTGEN-RAY TREATMENT

Patient, Med No Diagnosis	Date	Area Irradiated*	Reaction After Irradiation	Time of Bleeding in Relation to Treatment	Plasma CO ₂ Combining Power, Vol %
W J 16741 Carcinoma of prostate	9/21/21	Lower abdomen Lower abdomen Lower abdomen	Nausea, repeated vomiting, exacerbation of pain Slight anorexia, no nausea	Before	62.4
	9/24/21			6 hrs after	61.7
	10/13/21		22 hrs after	62.9	
	11/ 2/21		5 hrs after	61.1	
M R 16918 Carcinoma of ovary with ascites	10/20/21	Lumbar region Lower abdomen	Slight nausea, vomited once Nausea, vomited three times	Before	65.0
	11/ 5/21			3 hrs after	63.8
	11/23/21		2 hrs after	60.1	
	4/ 3/22	Lower abdomen	Nausea, repeated vomiting, reaction began before treatment was finished	2 mo after last treatment	52.8
	4/ 4/22			3½ hrs after	55.4

* These patients were treated by Dr. Lawrence Reynolds and received from 250 to 300 milliamperes minutes from a broad focus Coolidge tube activated by a Victor Snook interrupterless transformer with a spark gap of 9 inches between spheres, a target-skin distance of 12 inches and a filter of 0.5 mm of copper.

minutes were given, using a spark gap of 9 inches between spheres, a target-skin distance of 12 inches and a filter of 0.5 mm of copper. A few hours after the irradiation, during the reaction, blood was taken from an arm vein with a syringe and put into a tube containing a crystal of potassium oxalate. After centrifuging, the plasma was equilibrated with normal alveolar air and the carbon dioxide determined by Van Slyke's method (1917). No evidence of acidosis was found.

CONCLUSION

No evidence that the constitutional reaction following irradiation with roentgen ray is associated with a lowered alkali reserve was found in several determinations of the plasma carbon dioxide combining power of four patients and in repeated determinations of the plasma carbon dioxide content of three dogs.

I wish to thank Dr. Lawrence Reynolds, roentgenologist to the Peter Bent Brigham Hospital, for the use of roentgen-ray apparatus and to express my appreciation of the cordial cooperation of Prof. S. Burt Wolbach in checking up the pathologic findings and of Dr. G. H. Hansmann, resident pathologist, in the preparation of the pathologic material.

AN ANALYSIS OF SOME OF THE FACTORS OF VARIABILITY IN THE VITAL CAPACITY MEASUREMENTS OF CHILDREN *

D J EDWARDS AND MAY G WILSON
NEW YORK

The use of vital capacity measurements of the lungs in a comparative way implies a certain standard of reliability of the measurements on the normal subject. If the observations made on the normals cover a wide range of variability, then small differences, such as may well arise from moderate disturbances in function, will be obscured, and the practical value of the test greatly diminished.

In adults the limitations and practical usefulness of vital capacity measurements have been clearly shown in the work of Peabody,¹ West² and others. More recently, we have applied the test to children and have indicated a line of usefulness in this field.³ A question concerning the reliability of the results naturally arises, however, when vital capacity measurements are made on young subjects, since there are two outstanding ways in which the test, as applied to children, may be expected to yield more variable results than when applied to adults. First, the satisfactory performance of the test depends in large measure on an immediate and complete forcing-out of the air from the lungs when the test is made, and young subjects present some difficulty in getting a thorough expulsion of the air, and second, it is necessary to relate vital capacity to some other body measurement, such as height, weight, or body surface area, and during the growing period these body measurements are subject to marked change and individual differences.

The present study is an attempt to determine to what extent different methods of measuring the vital capacity influence the final values, and to define in a statistical way the amount of variability exhibited in a large series of vital capacity observations on children who were selected only with respect to the age limits of from 6 to 16 years and to clinically normal subjects.

Methods of Measuring the Vital Capacity—In a previous paper³ dealing with the vital capacity of children with heart disease we have given a figure representing the mean value obtained on a group of

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1 Peabody, F W, and Wentworth, J A. Arch Int Med **20** 443 (Oct) 1917.

2 West, H F. Arch Int Med **25** 306 (March) 1920.

3 Wilson M G, and Edwards, D J. Am J Dis Child **22** 443 (Nov) 1921.

normal subjects While this work was in print, Emerson and Green⁴ reported observations on the vital capacity of normal children of about the same age range that are significantly lower than those obtained by us We have, therefore, studied the matter further in an attempt to discover some of the reasons for the apparent difference in the two sets of observations Our observations were made with a specially constructed spirometer of the Gad-Krogh type In the calibration of this instrument the water displacement method was first used to measure off the liter divisions, and then the entire scale was checked against a ten liter Bohr meter A recalibration of the instrument has recently been made and this was found to confirm the original values We believe, therefore, that errors in calibration can be excluded as a possible cause for the higher values obtained by us

A second method of checking our results has been to compare the readings obtained with our instrument with those obtained on the same subjects with other spirometers Thirty-six subjects, ranging in size from 0.83 to 1.54 sq. m. surface area, were selected for the first series in the test The measurements of the vital capacity were taken on each subject with three spirometers and with only a few minutes intervening between each set of observations The instruments used beside our own were the Sanborn, made by the Sanborn Company, of Boston, and the Standard, made by the Narragansett Machine Company, of Providence The Standard instrument was calibrated by the same method as that described above and a corrected scale placed upon it

The Sanborn instrument gave results that agree very closely with those obtained with our instrument The average figure for the series shows a difference of a little less than 1.5 per cent, with the Krogh instrument giving the higher values When the results are arranged into groups on the basis of the surface area of the subjects there is shown a remarkable parallelism of the values obtained with these instruments throughout the size range With the Standard spirometer the results show consistently lower readings amounting to a difference of a little more than 10 per cent for the averages of the group, when compared with the figure obtained with our instrument There is also greater variation from group to group than is exhibited in the results with the other instruments

In another series of 115 cases we have compared the results obtained with other Standard spirometers (not calibrated by us) with those obtained with the Sanborn It should be noted, however, that the measurements in this series with the Standard instruments were not taken at the same sitting, but at a previous time ranging from a few

4 Emerson, P. W., and Green, H. *Am J Dis Child* 22:202 (Sept.) 1921

days to as much as a month. It will not be possible, therefore, to relate these values in a quantitative way. The significant feature in these results is the greater variability in the group averages given from the measurements with the Standard spirometer over those obtained on the same subjects with the Sanborn instrument.

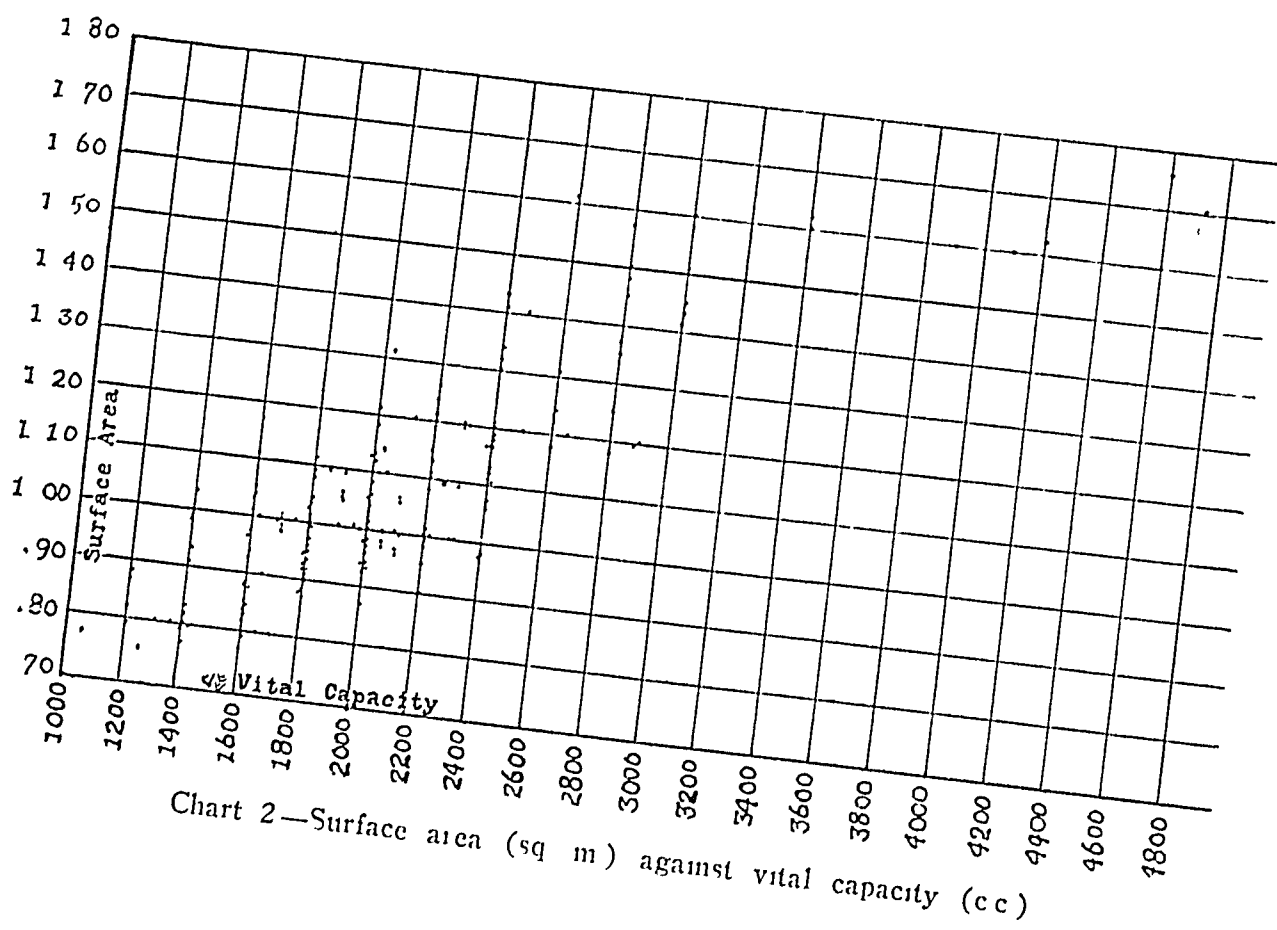
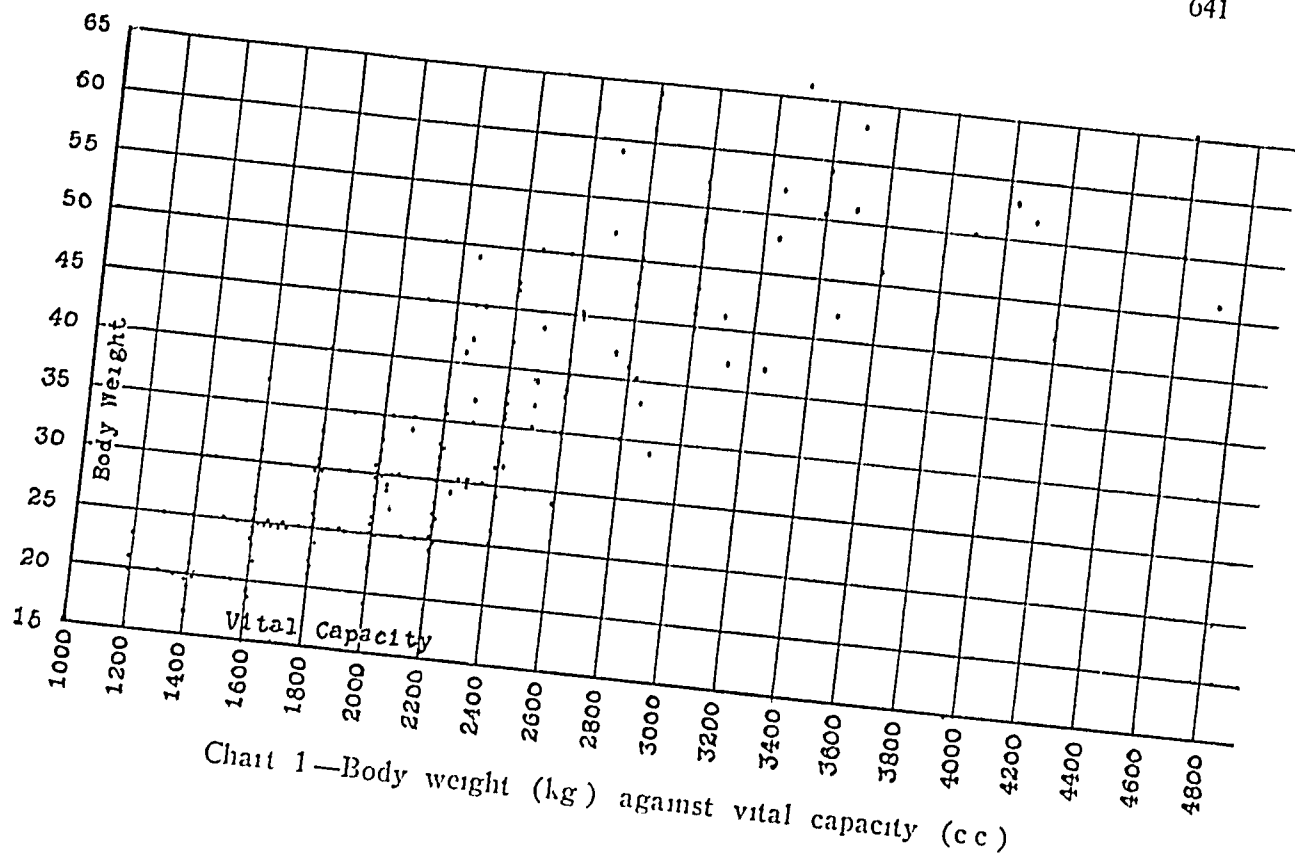
Another series of tests has been made, similar in procedure to the above, to compare the measurements obtained with a Dry spirometer made by Thomas Upham, of Boston, with those obtained with the Sanborn. Forty-one subjects were included in this series, and the average values for the group exhibit lower readings with the Dry spirometer by about 11.6 per cent. We are not justified in placing very much stress on this quantitative difference, since the measurements were not taken on the same date. But observations covering much longer intervals make it evident to us that the lower reading with the Dry spirometer cannot be explained on the basis of time changes.

It is indicated from these results that certain types of spirometers tend to give lower readings than others and that the group values obtained with the low reading spirometers generally exhibit greater variability. Differences of this character result in no small degree, we believe, from the use of instruments not sufficiently sensitive for the measurement of the vital capacity of children.

Another factor that appears to account for part of the discrepancy between the observations reported by Emerson and Green and those we have obtained is in the different method used for estimating the surface area. They employed, for the most part, the Benedict-Talbot method, whereas we have used exclusively the DuBois height-weight method. In order to obtain some notion of the extent of influence which this difference in the method of estimating the surface area might have on the final results, we selected at random ten cases published in the tables by Emerson and Green and have calculated these on the basis of the DuBois surface area chart. The results show an average about 12 per cent higher than their figures for the same subjects.

These considerations, while indicating two factors which make for the lower vital capacity values reported by Emerson and Green, do not account for the comparatively large difference between their findings and those we have obtained. If more complete data were available concerning technic and character of the subjects, it might suggest other factors that have contributed to the discrepancy, but in the absence of such material it is of no avail to speculate.

Variation of the Vital Capacity in a Group of Normal Subjects—In a group of thirty-five children in whom stem length, chest circumference, height, weight and vital capacity were taken we found³ that



in using Dreyer's⁵ standards for vital capacity the correlation to the surface area measurement (surface area calculated from the DuBois height-weight chart) appeared to be as close as that to any of the other body measurements. On the basis of this and also the work of West² and of Dreyer⁶ on adults, the surface area unit was adopted for relating all our vital capacity measurements. The work has been extended so that we now have records of the vital capacity, height and weight of 360 clinically normal children. This amount of material has seemed to warrant a closer study of the degree of variation exhibited, with a view to a more exact evaluation of its significance and better methods of expressing the results.

At present there is, in general, no better way of gaining a clear impression of the degree of variability of a series of observations

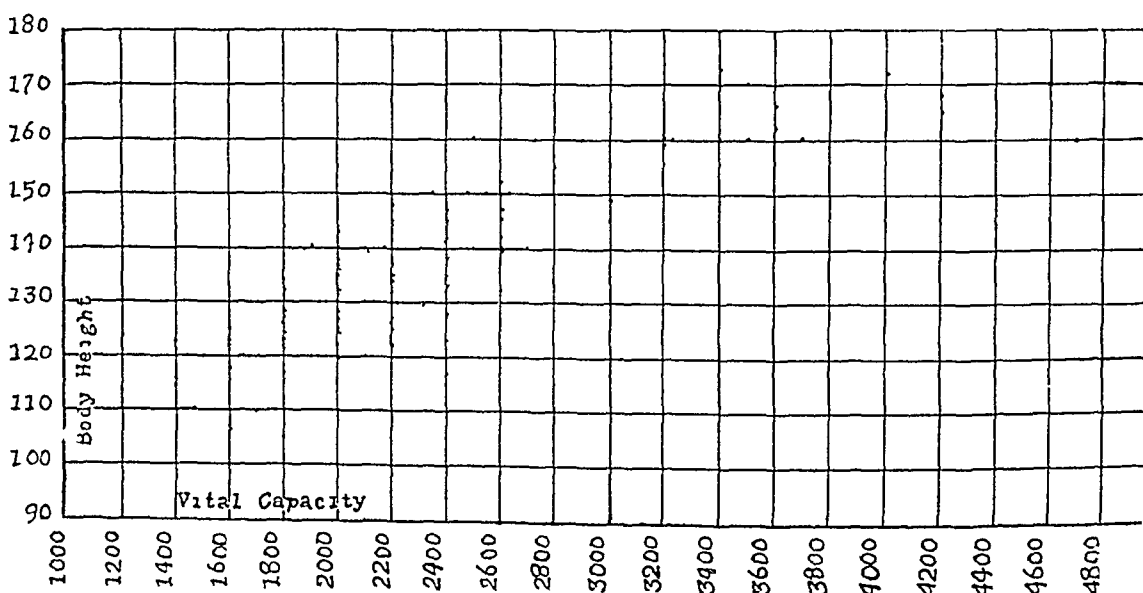


Chart 3—Body height (cm) against vital capacity (cc)

than to arrange them in the form of a plot. Although somewhat more time consuming, this method has the advantage of showing at a glance in which part of the range of variables there is present the greatest degree of scatter. In the present analysis the data have been arranged to plot the vital capacity as related to weight, to height and to body surface area.

An examination of these plots, shown in Charts 1, 2 and 3, reveals the greatest degree of scatter when the body weight is taken as the

⁵ Dreyer, G, in collaboration with G F Hanson. *The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body*, with Tables, Cassell and Company, London, New York, Toronto and Melbourne, 1920.

⁶ Dreyer, G. *Lancet* 1 197, 227, 1919.

measure of relationship, also that there is little difference between relating the vital capacity to surface area and that relating it to height alone. In the weight relation the greatest amount of scatter is shown by the measurements taken on the larger subjects. This we interpret to mean that the factors which make for variability in weight are operative to a greater extent in children weighing more than 40 kg.

The plot for the height relation shows a fairly well grouped set of observation throughout the range. The method of relating the vital capacity to surface area presents a close correlation in that part comprising the smaller subjects, but, like the weight relation, shows divergence as we approach the higher vital capacity readings from larger subjects. This feature of the surface area relation naturally follows from relations previously shown for the height alone and for the weight alone, since the method of deriving surface area contains an element of both factors.

In the light of these results, the method of relating the vital capacity to a body height measurement seems indicated as a general practical procedure. This does not imply that the vital capacity measurement in children is more closely correlated to body height than it is to surface area as we have derived the latter, but it is interpreted rather to indicate that the inherent errors in the weight measurement, when deductions have to be made for clothing, and the accumulative errors, when surface area calculations are carried out from these measurements, more than offset the slight difference in absolute correlation which the surface area relation may contain.

In turning now to the problem of the closeness of correlation of the vital capacity to the surface area it will be important to remember that our subjects present a normal group from an ordinary clinical standpoint. Beyond this it is impossible to speak with exactitude in regard to their soundness, in fact, in the light of more recent work, there is reason for believing that a small percentage of the group would reveal abnormal conditions with more exact methods of diagnosis. It is of interest to note, therefore, that the standard deviation of this series, which gives a measure of the variability in terms of the unit in which the variable is measured, i. e., in liters vital capacity per square meter body surface area, is 0.272 for the 360 cases. To obtain a measure in relative terms of the variability of different characteristics measured, it is customary to express them as percentages of their individual means. This coefficient of variation ($C \text{ of } V = \frac{100 \sigma}{\text{mean}}$) in the present series is found to be 14.2 per cent.

In variability, as measured in the absolute terms of the standard deviation and in the derived relative term of the coefficient of variation, our series shows a value slightly greater in magnitude than certain

other physiological measurements, such as the pulse rate and the heat production in adults,⁷ but it is less than that reported on such measurements as keenness of sight⁸ and heat production in infants⁷

The results of this brief comparison indicate that our series shows a satisfactory agreement with the results of others on fairly comparable physiological measurements. The agreement seems rather remarkable when one considers the probable influence of age, sex, race, the small percentage of cases not strictly normal, and the differences in mental cooperation in the test.

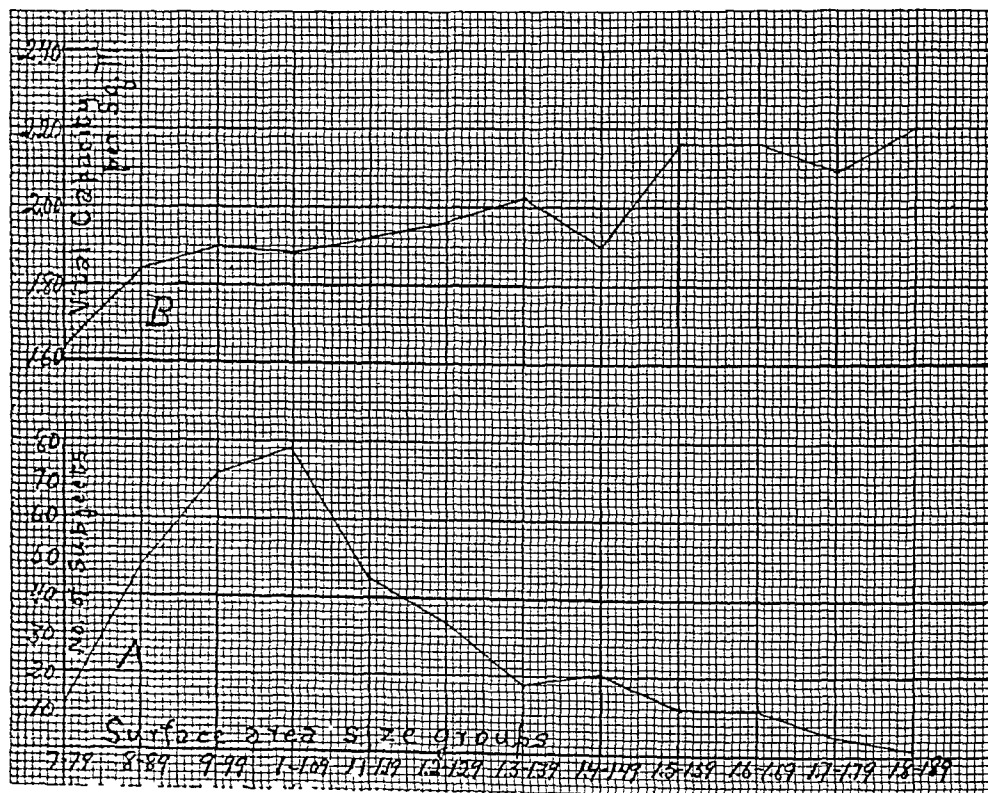


Chart 4—(A) Distribution of subjects grouped according to surface area size (B) Average vital capacity of each group in surface area size arrangement

Vital Capacity as Related to Body Size—In the course of these observations on the vital capacity of children, as related to surface area, we have been impressed by the frequency with which low readings were obtained on small children, and similarly a tendency for larger subjects to give higher readings.

The surface area measurement, containing as it does a height and weight element probably expresses more exactly than any other body

⁷ Harris I A, and Benedict F G. Carnegie Institution of Washington, Pub 279 1919

⁸ Pearson K. The Chances of Death and Other Studies in Evolution, E Arnold London 1897

measurement the body size relation of groups of subjects differing markedly in their individual proportions. On the basis of this conception of body size, we have divided the whole range of our 360 cases into groups of convenient units as regards their surface area size. Each subject was then assigned to the appropriate group with his vital capacity calculated on the basis of his surface area. The mean value for each group was then determined with a view of showing to what extent size introduces a variable in a statistical average for the whole series.

The results of this method of analysis are very well brought out in Chart 4. The curve at the bottom (A) shows the frequency distribution in terms of the group totals. It exhibits a skew type of curve with the mode at about 1 sq. m. surface area size. This form of the curve merely signifies that, in selecting our subjects from the ages of six to sixteen, inclusive, we have inadvertently obtained a preponderance of subjects in the lower half of the range. The upper curve (B) of the mean vital capacity for each size group shows a distinctly upward trend from the smaller to the larger sized subjects. The slope of the curve suggests that, with a larger number of cases, it would give a straight line cutting approximately the point 1.74 at the lower, and 2.18 at the higher range. This would give roughly a 25.2 per cent. range, which is probably statistically significant. It indicates that in the evaluation of an individual vital capacity measurement on the basis of surface area some account has to be taken of the actual size of the subject measured before an accurate estimate of the deviation from the normal can be made. It follows, therefore, that a single mean value derived from a large group of widely differing sizes of children offers only an approximation to the true mean of any individual class.

It is of interest in this connection to consider the possible meaning of the type of curve presented by this method of grouping according to body size. There is suggested the operation of at least three factors, either separately or in common. First, the method of deriving surface area may contain an element of inaccuracy with diminishing stature, second, the method of measuring the vital capacity may similarly introduce a constantly increasing error with smaller subjects, and third, the vital capacity in terms of its absolute relation to body size may undergo an increase in children as they approach maturity. The data at hand afford no basis for determining the degree of operation of these different factors.

It is pertinent to this discussion to note that in the grouping of the subjects according to the surface area size there is naturally a certain amount of segregation of age relations. The subjects comprised, for example, in the group from 0.7 to 0.79 sq. m. surface area,

are as a group younger than those included in the group from 120 to 129 sq m. An analysis of these group results will show, therefore, whether less variability goes with greater maturity and stature. If we use as a measure of variability the coefficient of variation, it is evident from the accompanying table that the small young subjects do not give values significantly more variable than shown by the older and larger subjects.

THE VARIABILITY OF THE VITAL CAPACITY MEASUREMENTS SHOWN BY DIFFERENT GROUPS ARRANGED ACCORDING TO SURFACE AREA SIZE

Group	No of Cases	Maximum	Minimum	Percentage Range	Mean	Standard Deviation	Coefficient of Variation
0.7-0.79	12	2.97	1.28	61.8	1.64	0.233	14.2
0.8-0.89	49	2.35	1.37	71.5	1.84	0.252	13.9
0.9-0.99	72	2.44	1.42	71.8	1.90	0.220	11.6
1.0-1.09	79	2.34	1.33	76.0	1.89	0.237	12.5
1.1-1.19	45	2.38	1.33	79.0	1.92	0.232	12.1
1.2-1.29	34	2.30	1.41	63.0	1.96	0.234	11.9
1.3-1.39	18	3.10	1.41	120.0	2.02	0.260	12.9
1.4-1.49	22	2.36	1.54	53.0	1.90	0.203	10.7
1.5-1.59	12	3.23	1.48	118.0	2.18	0.350	16.0
1.6-1.69	12	2.88	1.52	89.5	2.18	0.500	22.9
1.7-1.79	5	2.77	1.57	76.5	2.09	0.248	11.9

These results support the conclusion that the observations made on small young children are statistically as reliable as those obtained from the more mature subjects, moreover, they indicate that the lower mean values shown in the curve of Chart 4 for the subjects of small surface area size are probably not due to an error inherent in the method, which is inversely related to size and age of the subjects measured.

SUMMARY

The measurement of the vital capacity of children with certain types of spirometers has given results 10 per cent or more below that obtained on the same subjects with other instruments. Moreover, the results obtained with those instruments giving low readings exhibit a greater degree of variability. It is suggested that the low readings of a more fluctuating character are probably due to the use of a spirometer not sufficiently sensitive for the measurement of the vital capacity of children.

The vital capacity observations on 360 normal children, when related separately to the body measurements, height, weight and surface area, exhibit a correlation slightly to the advantage of the height relation. It is suggested that the height unit may be the most practical body measurement for the relating of the vital capacity of children, not that the absolute correlation is greater than the surface area unit, but rather that the chances for errors in the calculations are less and in practice will more than offset any fundamental difference there may be in favor of the surface area method.

The absolute variability in this series, as shown by the standard deviation, is 0.272 liters per square meter surface area. The coefficient of variation is shown to be 14.2 per cent, a value agreeing fairly well with that of other physiological variables of a comparable nature.

Based on the surface area measurement as a criterion of body size, certain groupings have been made. The mean vital capacity of each of these groups was obtained, and from these data it has been shown that the vital capacity, as related to a unit of surface area, exhibits gradually increasing values from the smaller to the larger-sized subjects. This difference is estimated to be of the order of a 25 per cent range for the size groups.

In terms of the coefficient of variation, the groups comprising the smaller surface area size, which were likewise made up of younger subjects, do not exhibit greater variability than the groups of larger surface area size made up of older subjects. It is argued that the age factor does not make for greater variability in the measurement of the vital capacity of children.

CONCLUSIONS

1. A spirometer that offers minimal resistance to the egress of the air from the lungs is necessary for measuring the vital capacity of children.

2. The correlation between vital capacity and body height is more intimate than that between vital capacity and surface area, or body weight.

3. The vital capacity values obtained from children show a degree of variability about equal to that exhibited by other fairly comparable physiologic variables. Young children give results that are not more variable than those from older ones.

4. Children of small stature exhibit a lower vital capacity per unit of surface area than those of larger stature.

STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE

VI THE SIGNIFICANCE OF THE VITAL CAPACITY TEST IN PULMONARY TUBERCULOSIS, BRONCHIAL ASTHMA, PNEUMONIA AND AN ACUTE INFECTION OUTSIDE THE RESPIRATORY TRACT [†]

J A MYERS, M D
MINNEAPOLIS

In the last decade, particularly the latter half of this decade, the vital capacity test, together with certain measurements of the body from which physical fitness is ascertained, has rapidly been gaining in favor with physicians especially interested in diseases of the heart and lungs. The present study of which this paper is only a preliminary report represents an attempt to investigate carefully the value of the vital capacity test in diseases of the lungs.

Recently I reported ¹ approximately 100 cases in all of which stereo-roentgenograms were made. Later ² I reported 230 cases. Since these papers were prepared further data have been collected and compiled on cases of pulmonary tuberculosis, bronchial asthma, pneumonia and one acute infection outside the respiratory tract (paratyphoid fever).

I PULMONARY TUBERCULOSIS

The present report details the findings in 335 cases. Unfortunately roentgenograms could be had in only 210 cases. In all other cases the remaining necessary aids in diagnosis were employed and there was finally no doubt as to the diagnosis in any case.

Table 1 shows that on a basis of the roentgen-ray examination the cases were classed as follows: I Suspected cases. A Roentgen-ray examination negative. II Tuberculous cases. A Peribronchial tuberculosis, (1) unilateral, (2) bilateral. B Parenchymatous tuberculosis, (1) unilateral (a) disease confined above the first rib or an area of similar size, (b) disease extending below the first rib, but not involving more than one lobe, (c) involvement of more than one lobe,

* From the Department of Internal Medicine, University of Minnesota, and the Tuberculosis Department of the Minneapolis General Hospital.

* Read in part before the ninth session of the Mississippi Valley Conference on Tuberculosis, Columbus, Ohio, Sept. 12-14, 1921.

1 Myers, J. A. IV A Comparison of Vital Capacity Readings and Roentgen-Ray Findings in Pulmonary Tuberculosis, Tr. National Tuberculosis Association New York, June, 1921, A. Rev. Tuberc. 5, 1922.

2 Myers, J. A. V A Comparison of Vital Capacity Readings and Physical Signs in Pulmonary Tuberculosis. Minnesota Med. 5 233 (April) 1922.

(2) bilateral (*a*) disease confined above the first rib or an area of similar size on each side, (*b*) disease extending below the first rib on each side but not involving more than two lobes, (*c*) involvement of more than two lobes

There are thirty suspected cases in which the roentgenograms showed no evidence of disease. The mean vital capacity percentage for this group is 102, while the range is between 82 and 122 per cent.

The group in which roentgenograms revealed unilateral peribronchial tuberculosis consists of thirty-one cases. The average vital capacity for this group is 96 per cent and the range is from 81 to 121 per cent. There are only eight cases of bilateral peribronchial tuberculosis in the group and their mean vital capacity percentage is 102, while the range is between 87 to 112 per cent.

Thirty-three cases showed unilateral parenchymatous tuberculosis above the first rib or a single area of similar size in some other part

TABLE 1—CLASSIFICATION OF CASES ON BASIS OF ROENTGEN-RAY EXAMINATION

	Number of Cases	Vital Capacity Percentage		
		Average	Lowest	Highest
I Suspected cases				
A Roentgen ray negative	30	102	82	122
II Tuberculous cases				
A Peribronchial tuberculosis				
1 Unilateral	31	96	81	121
2 Bilateral	8	102	87	112
B Parenchymatous tuberculosis				
1 Unilateral				
(a) Above first rib	33	96	74	119
(b) No more than one lobe involved	23	87	31	122
(c) More than one lobe involved	15	65	38	106
2 Bilateral				
(a) Above first rib	15	86	51	108
(b) No more than two lobes involved	30	73	43	119
(c) More than two lobes involved	25	54	26	82

of the lung. The average vital capacity for this group is 96 per cent, but the range is between 74 and 119 per cent. There is a group of twenty-three cases with more extensive disease than the last group mentioned but in no case does the involvement extend over more than one lobe. This group shows an average vital capacity of 87 per cent with a range of from 31 to 122 per cent. There are only fifteen cases in the group in which the roentgenograms show unilateral disease involving more than one lobe. The average vital capacity for this group is 65 per cent, while the range is from 38 to 106 per cent.

The group of fifteen cases in which the roentgenograms show disease limited to that part of each lung above the first rib or an area of similar size on each side presented an average vital capacity of 86 per cent with a range of from 51 to 108 per cent. In the next group, which consists of thirty cases with involvement limited to one lobe on each side, the average vital capacity is 73 per cent, while the range is from 43 to 119 per cent. It is not surprising to find that

the last group, consisting of twenty-five cases with disease involving more than two lobes, presents the lowest vital capacity percentage. The average for this group is 54 per cent, while the range is from 26 to 82 per cent.

On the basis of the physical examination, the patients were grouped as follows: I Suspected cases, (a) no physical signs, (b) physical signs indefinite (diagnosis reserved). II Definitely tuberculous cases, (a) minimal disease, (b) moderately advanced disease, (c) far advanced

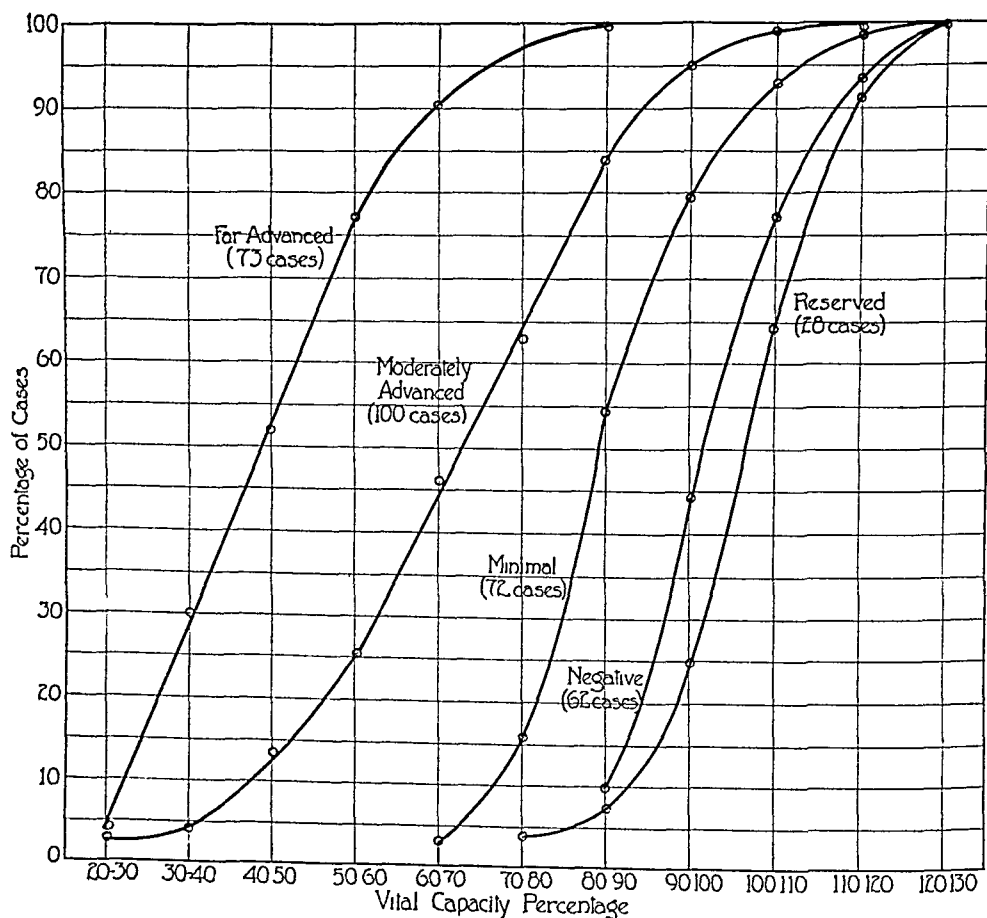


Fig 1—Ogive curves showing percentage of cases in each stage plotted against the percentage of vital capacity

disease. Ogive curves (Fig 1) were made in order to facilitate in the visualization and analysis of the data in each group of cases.

From these curves it will be seen that the range of vital capacity percentage is indicated in each group. For example, along the curve representing the far advanced cases we see within the from 20 to 30 per cent vital capacity percentage line a small circle. This circle lies at a height representing approximately 4 per cent of the cases studied. This means that approximately 4 per cent of the far advanced cases

had vital capacities as low as 20 per cent of the normal. If we pass upward along the curve we find another circle lying within the from 30 to 40 per cent vital capacity percentage line and within the horizontal line representing 30 per cent of the cases. Here we have added together all the cases with a vital capacity below 30 per cent of the normal and it is obvious from the curve that approximately 30 per cent of the far advanced cases have such reduced vital capacities. Such information may be obtained, all along the curve. The last circle at the upper end of the curve lies within the vertical line representing the from 80 to 90 per cent vital capacity group. This circle also lies within the horizontal line representing 100 per cent of the cases. It is, therefore, obvious that all of the far advanced cases have vital capacities below 90 per cent of the normal.

From the use of these curves similar information may be obtained regarding the percentage of vital capacity in the moderately advanced, minimal, reserved and negative cases. One may ascertain quickly the vital capacity percentage of any given percentage of cases in all the

TABLE 2—VITAL CAPACITY IN CASES OF THICKENED PLEURA, CAVITATION AND PNEUMOTHORAX

	Number of Cases	Vital Capacity Percentage		
		Average	Lowest	Highest
Cases with thickened pleura revealed by roentgen-ray examination	12	78	30	115
Cases with cavities revealed by roentgen ray examination	30	64	31	109
Cases with pneumothorax	9	49	32	58

groups. If, for example, a horizontal line (a) is drawn representing 50 per cent of the cases through all the curves it is seen that 50 per cent of the far advanced cases have a vital capacity from 40 to 50 per cent of the normal, while the remaining 50 per cent have a higher vital capacity percentage. This horizontal line intersects the curve representing the moderately advanced cases slightly beyond the vertical line representing from 60 to 70 per cent vital capacity, therefore, approximately 50 per cent of the moderately advanced cases have vital capacities within or below from 60 to 70 per cent of the normal. Further observation will show that approximately 50 per cent of the minimal, negative and reserved cases have vital capacities within or below from 80 to 90, from 90 to 100 and from 100 to 110 per cent of the normal, respectively.

In Table 2 the cases with thickened pleura revealed by roentgen-ray examination, cavitation revealed by roentgen-ray examination and pneumothorax (spontaneous and artificial) are grouped separately. There are only twelve cases in the group in which the roentgen ray revealed thickened pleura. Some of these cases have insignificant

pulmonary lesions while others have far advanced lesions of tuberculosis. The average vital capacity for the series is 78 per cent, while the range is from 30 to 115 per cent. It is interesting to note that in some cases with very slight pulmonary involvement the vital capacity is not at all or very slightly reduced. There are thirty cases in the group in which the roentgen-ray examination revealed pulmonary cavities. For this group the average vital capacity percentage is 64 while the range is from 31 to 109 per cent. The nine cases with pneumothorax show about what one might expect, that is, a reduction in vital capacity of approximately 50 per cent. The actual average for this group is 49 per cent, while the range is from 32 to 58 per cent.

The tables and curves show that those patients whose roentgenograms do not reveal disease have an average vital capacity of approximately 100 per cent. There are a few cases in this group with vital capacities slightly below normal. In most cases of this kind the reduction can be accounted for on the basis of such factors as age and obesity. There are several cases in this group with an overdeveloped vital capacity due to previous special training, hence their vital capacities are above 100 per cent.

The cases with peribronchial tuberculosis were found to have an average vital capacity which very nearly approaches 100 per cent. This average and the range of vital capacity does not differ much from the cases in which the roentgen ray did not reveal disease. It is interesting to note that those cases with bilateral peribronchial tuberculosis have an average vital capacity percentage which is higher than that of those cases with unilateral peribronchial tuberculosis.

In the thirty-three cases with parenchymatous lesions above the first rib on one side, the average vital capacity percentage is well within the normal limits. The low limit of the range in this group, however, is as low as 74 per cent of the normal. From this small number of observations it appears that tuberculous lesions (although very small) of clinical significance reduce the vital capacity. On the other hand, there are several cases in this group with vital capacities above 100 per cent. It should be stated that in a few of these cases the roentgen-ray examination revealed only small areas of calcification or fibrosis. For example, in one case a fluoroscopic examination revealed a dark area about the size of a walnut in the region of one of the basal lobes. The examining physician being willing to make a diagnosis of early tuberculosis without the aid of stereoscopic plates and without a careful study of the symptoms sent this patient to a sanatorium for treatment. After admission to the sanatorium stereoscopic plates revealed evidence of a small area of calcification in one basal lobe. The remainder of both lungs was clear. This patient did not have one of the cardinal symptoms of tuberculosis and presented a vital capacity of 100 per cent.

Another patient whose stereoscopic plates now show evidence of a definite tuberculous infiltration was treated in a sanatorium three years ago. He has been working for the past two years and now, in spite of the roentgen-ray findings, has a vital capacity of more than 100 per cent.

In the group (Table 1) with more extensive unilateral disease, the average vital capacity percentage decreases, however, even in those cases with involvement of more than one lobe there is an occasional case with a vital capacity of 100 per cent or more.

In the group of cases with bilateral disease there are fifteen with disease only above the first ribs. As might be expected, the average vital capacity percentage of this group is somewhat higher than in the group of unilateral cases with involvement of more than one lobe. Here, too, there are cases with only calcified or fibrous tuberculous processes limited to the extreme apices. Attention should be called to the fact, however, that while a few cases in this group have vital capacity percentages within normal limits, there are others with more severe disease with a vital capacity as low as 51 per cent of the normal.

In the remaining groups of cases with bilateral disease the average vital capacity percentage decreases as the extent of involvement revealed by the roentgen-ray increases.

More than 100 ex-service men are included in this study. It is interesting to note that many of these men are included in the groups showing (*a*) signs of minimal disease, (*b*) indefinite signs, and (*c*) no signs of disease. In a considerable number of cases the roentgen ray revealed evidence of slight parenchymatous disease above the first rib on one or both sides, peribronchial tuberculosis, or no evidence of disease. In view of these facts, the ex-service men show a rather high average vital capacity percentage. In civil life patients often come late for diagnosis possibly because of the physician's fee, or many have dependents to support and do not give up work until forced to do so by moderately or far advanced disease. In the case of ex-service men the government provides for transportation, free examination, free observation and treatment, and compensation in cases of active disease traceable to service. Under these conditions very few men have a fear of a diagnosis of tuberculosis, and, in fact, a few desire it. This condition is making possible the diagnosis of many early cases of pulmonary tuberculosis. On the other hand, some cases of slight and insignificant lesions of long standing are being diagnosed and placed in hospitals for treatment and recommended for compensation.

We have seen that a considerable number of cases with signs of minimal and moderately advanced disease, many of whom are confirmed by stereoroentgenograms, show a vital capacity percentage within normal limits. This fact may be explained in one or all of the following three ways. (1) We know that some of these patients had over-

developed vital capacities, and although they are now reduced considerably they still have capacities which appear to be within normal limits (2) A few of the patients have tuberculous lesions which are very definite, although at present they are clinically insignificant The percentage of cases which fall into this class will be ascertained only through further observation over a considerably longer period of time (3) There is some evidence to suggest that the normal standards now employed are not quite applicable for the people of all parts of the United States Dreyer's work³ was carried out in England and the normal standards derived from his formulas are mostly commonly used today Dreyer suggests, however, that the normal standards be ascertained for the people of various countries Heise⁴ in reporting the vital capacity findings on sixty-five patients in the Trudeau Sanatorium remarked that the test was not of great value to him as many patients had vital capacities within normal limits Many of my vital capacity percentages also have seemed too high From the present evidence it would appear that the people of the United States, particularly of the Middle West, have a greater vital capacity than the people of England I have already⁵ undertaken to throw some light on this subject, not by the use of mathematical formulas alone, but by actual observations made on several thousand individuals in various occupations Observations have already been made on several hundred persons and the accumulation, compilation and analysis of these data are proving to be a tremendous task, the completion of which will require a long period of time

SUMMARY

1 Vital capacity readings were taken in 335 cases suspected of having pulmonary tuberculosis Stereoscopic plates were made in 210 cases

2 In thirty cases in which stereoroentgenograms showed no evidence of disease the mean vital capacity was 102 per cent of the normal, while the range was between 82 and 122 per cent of the normal

3 Dreyer, G Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, *Lancet* **2** 227 (Aug 9) 1919 Dreyer, G and Burrell, L S T The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, *Lancet* **1** 1215 (June 5) 1920 Dreyer, G The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body Paul B Hoeber, New York City, 1921

4 Heise, F H Tr National Tuberculosis Association, 1921, p 140

5 Myers, J A Studies on the Respiratory Organs in Health and Disease II A Study of the Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness, *Journal-Lancet* **41** 252 (May 1) 1921 III The Value of Vital Capacity Readings in Clinical Medicine, *Minnesota Med* **4** 635 (Nov) 1921

3 The stereoroentgenograms showed peribronchial tuberculosis in thirty-nine cases. The average vital capacity of these cases was 97 per cent and the range was from 81 to 121 per cent of the normal.

4 There were seventy-one cases with unilateral and seventy cases with bilateral parenchymatous tuberculosis revealed by the stereoroentgenograms. These cases were grouped according to the extent of disease revealed. Among these groups the vital capacity percentages were usually found to decrease as the extent of the disease increased.

5 On the basis of the physical examination, sixty-two cases showed no evidence of pulmonary tuberculosis. Ten per cent of these cases had a vital capacity between 80 and 90 per cent of the normal while the remainder were all well within the normal limits.

6 There were twenty-eight cases in which physical signs caused the diagnosis to be reserved. Approximately 4 per cent of these patients had vital capacities between 70 and 80 per cent of the normal, and approximately 3 per cent more had vital capacities between 80 and 90 per cent of the normal. The remainder of these were within normal limits.

7 There were signs of minimal tuberculosis in seventy-two cases, moderately advanced tuberculosis in 100 cases, and far advanced tuberculosis in seventy-three cases. In the majority of cases the vital capacity was found to be decreased in proportion to the extent of involvement revealed by the physical signs.

8 Pulmonary cavities were revealed by the roentgen ray in thirty cases. The mean vital capacity for this group was found to be 64 per cent, while the range was between 31 and 109 per cent of the normal.

9 Nine cases had spontaneous or artificial pneumothorax. The mean vital capacity of this group was 49 per cent while the range was between 32 and 58 per cent of the normal.

2 BRONCHIAL ASTHMA

Staehelin and Schutze,⁶ Plesch,⁷ Peabody and Wentworth,⁸ and others, have reported vital capacity findings in patients suffering from asthma. In some cases the vital capacity was considerably decreased while in others it was normal.

In this study observations were made on twenty persons suffering from bronchial asthma. Readings were taken during and at various

6 Staehelin, R., and Schutze, A. Spirographische Untersuchungen an Gesunden, Emphysematikern und Asthmatikern, *Ztschr f klin Med* **75** 15, 1912.

7 Plesch, J. Die pathologische Physiologie des Lungenvolumens und seine Beziehung zum Kreislauf, *Ztschr f Exper Path u Therap* **13** 165, 1913.

8 Peabody, F. W., Wentworth, J. A., and Barker, B. I. Clinical Studies on Respiration, *Arch Int Med* **20** 433, 443, 468 (Sept) 1917. McClure, C. W., and Peabody, F. W. *J A M A* **69** 1954 (Dec 8) 1917.

intervals between acute attacks During acute attacks the vital capacity was found to be tremendously reduced, in some cases being as low as from 18 to 20 per cent of the normal With the disappearance of the attack, however, the vital capacity quickly returned to normal limits unless there existed some complication or other cause for a reduction Different methods of treatment were employed, for example, some patients were given vaccines, others were given expectorants and in still others dietetic treatment was ordered In most cases the vital capacity remained normal as long as the chest was kept free from râles There were four cases in which asthma had extended over a period of many years In none of these cases did the vital capacity return to normal limits after the disappearance of the asthmatic attacks In each case the physical and roentgen-ray examinations revealed definite evidence of emphysema which was apparently sufficient to account for the reduced capacity Three patients were beyond the age of 50 None of these quite returned to normal after the subsidence of their acute attacks Since vital capacity decreases after the age of 40 or 50, the slight permanent reduction in these three cases was explainable on the age basis The remaining cases showed vital capacities well within normal limits soon after the acute attacks had subsided

SUMMARY

- 1 Vital capacity readings were taken in twenty cases of bronchial asthma
- 2 The vital capacity was greatly reduced during acute attacks In some cases it was reduced to from 18 to 20 per cent of the normal
- 3 After acute attacks subsided the vital capacity returned to normal in all cases except four with emphysema and three beyond the age of 50

3 PNEUMONIA

In five convalescent cases of pneumonia Peabody and Wentworth⁸ found the vital capacity to be between 71 and 114 per cent of the normal In only one of these cases, however, was there evidence of pulmonary involvement when the readings were taken The authors call attention to the fact that in the cases which were below normal one must take into consideration the general weakness persisting after an acute infection They also call attention to the difficulty experienced in taking lung capacity readings in cases suffering from pleurisy

In the present work an attempt was made to study the lung capacity throughout the course of the disease, and, finally, to make a correlation of the patient's temperature, pulse, respiration and vital capacity at different stages Observations were made on twenty patients The

measurements and readings were taken in the usual manner, and the vital capacity percentages were calculated as previously described⁵ In a few of the cases the crisis occurred about the time the patients were admitted to the hospital or before observations were begun In these

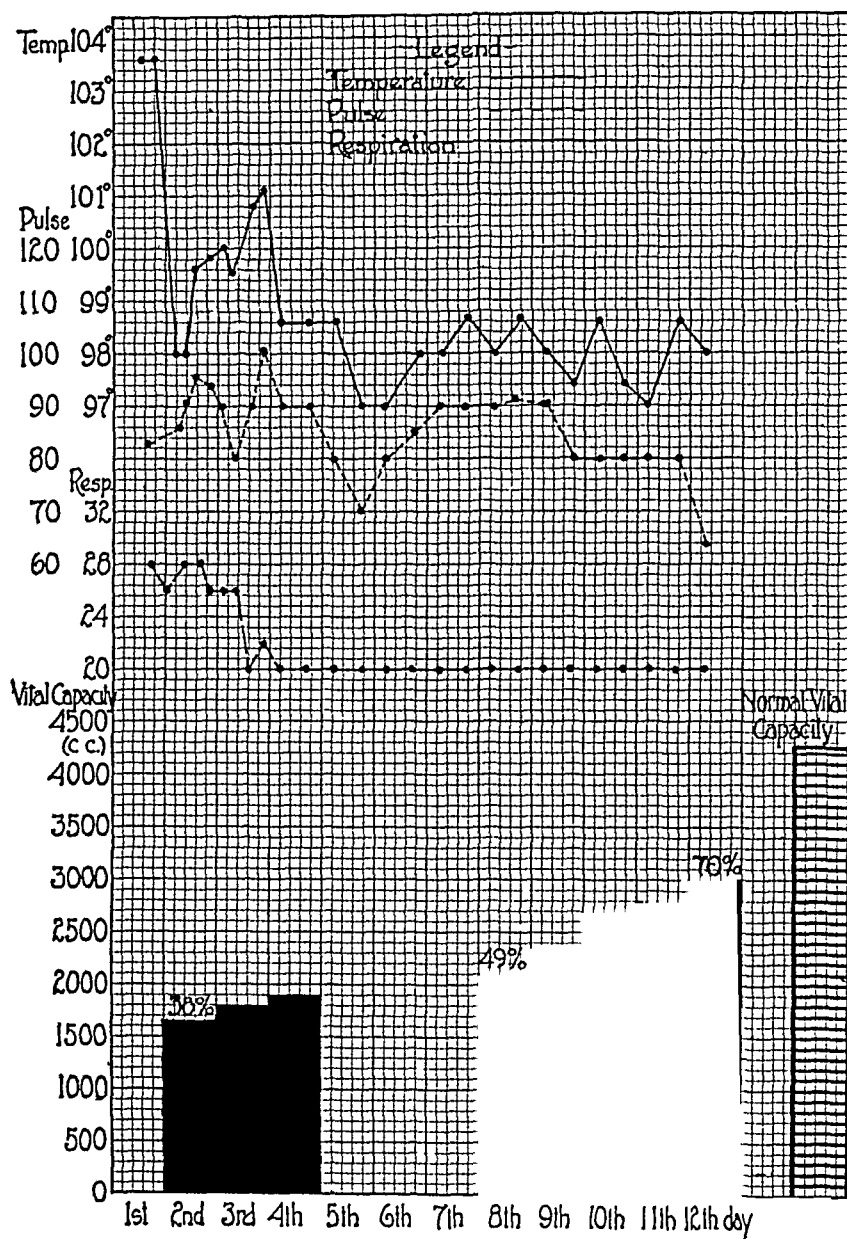


Fig 2—Temperature, pulse, respiration, and vital capacity curves in the case of a man, aged 58 (colored), suffering from lobar pneumonia involving the left lower lobe Left hospital on the twelfth day with the vital capacity 70 per cent of the normal

cases, therefore, the study could be carried out only during convalescence In a few other cases it was possible to begin the observations before any physical signs of pneumonia could be elicited There was an occasional case omitted in which it was impossible to get accurate readings on account of severe pleurisy

The curves (Figs 2 to 7) show the temperature, pulse, and respiration for each day and the vital capacity readings on days when it was advisable to take such readings. In the last column of each chart is indicated the theoretical normal vital capacity for the given case. At

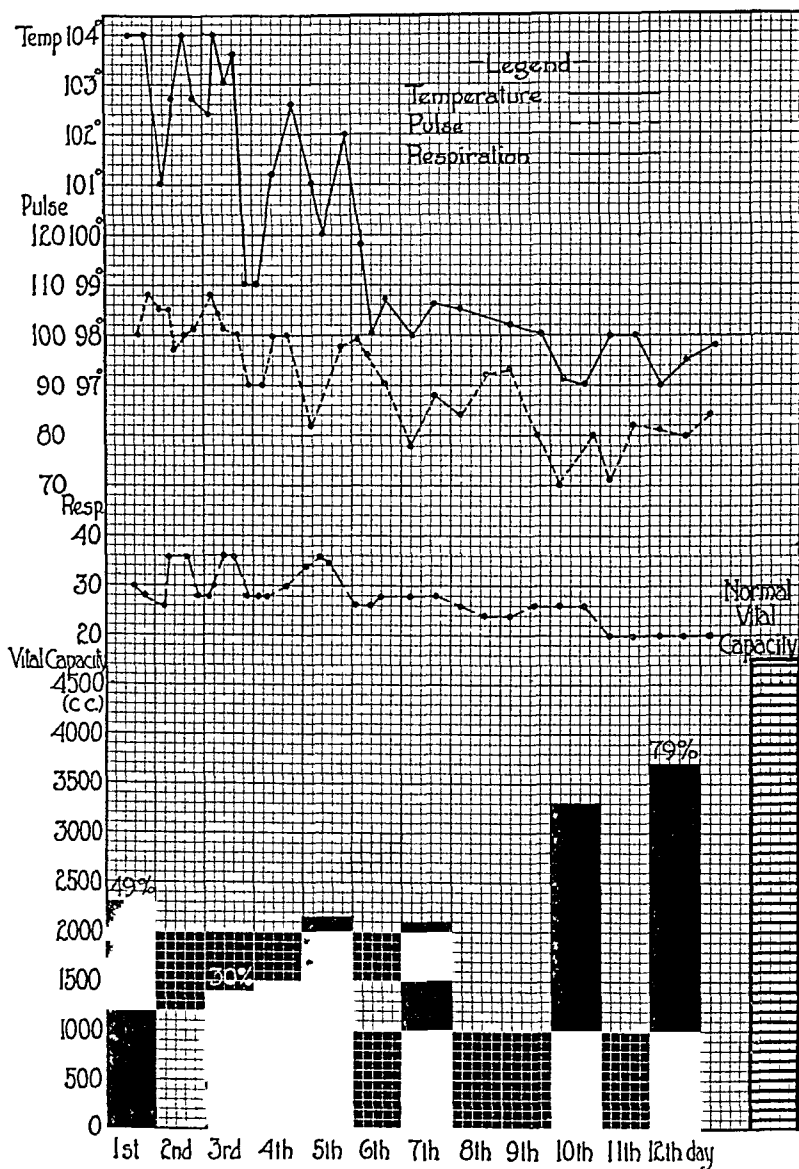


Fig 3—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 44, suffering from broncho-pneumonia with areas of involvement in both lower lobes. Left hospital on twelfth day with the vital capacity 79 per cent of the normal.

the top of certain columns representing vital capacity is placed the vital capacity percentage of the patient for that day.

In observing the curves it is interesting to note that the vital capacity is very low from the beginning, in fact it is reduced to 50 per cent or

less in most cases. This marked reduction of vital capacity from the beginning of a case of pneumonia is almost diagnostic. I have been able to go through good sized wards where the patients were suffering from acute disease (other than pneumonia) of the respiratory and

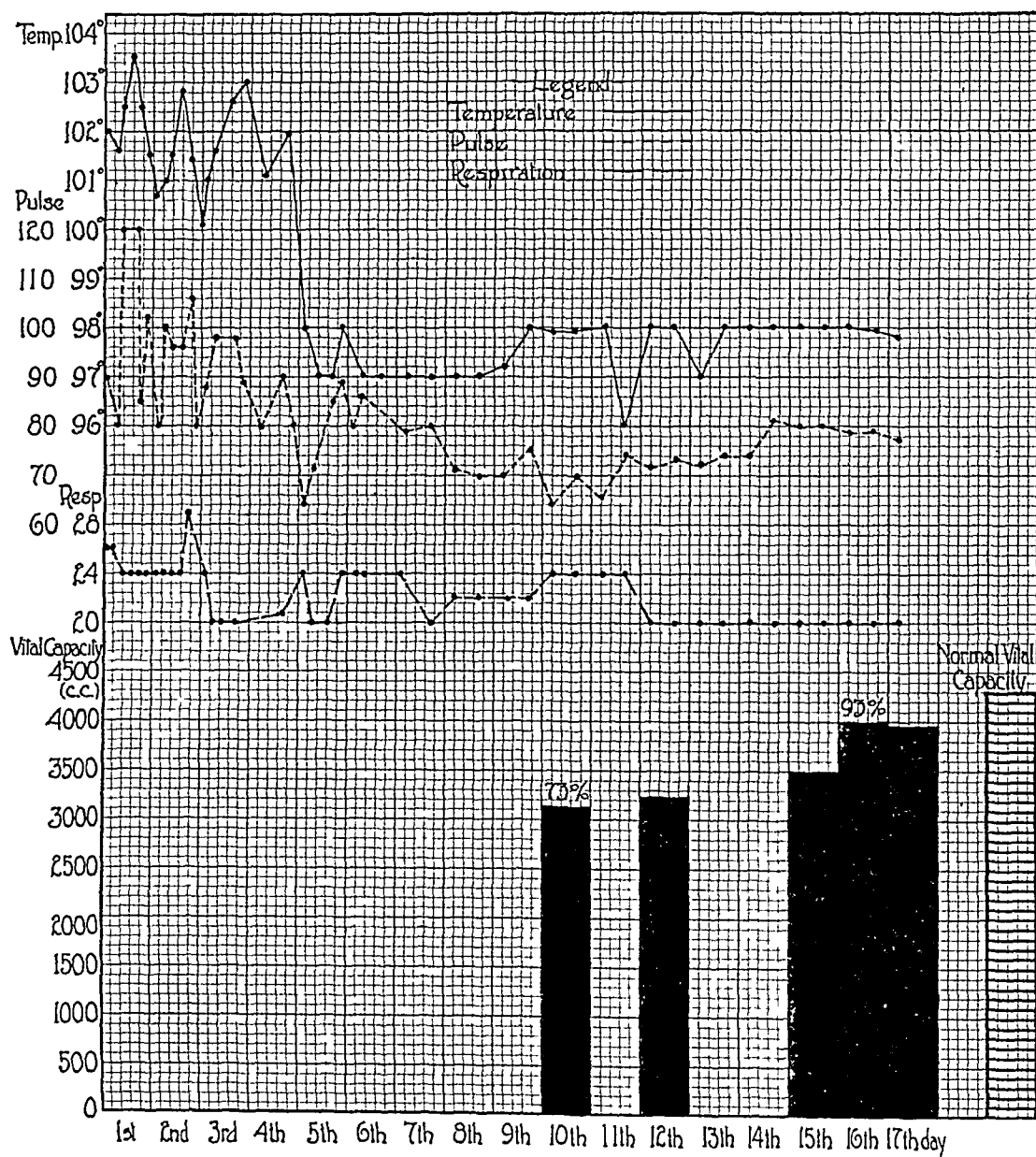


Fig 4—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 42, suffering from lobar pneumonia involving the right lower lobe. Left hospital on the seventeenth day with the vital capacity approximately 93 per cent of the normal.

other organs, calculate vital capacity percentages of the patients and select all the cases on whom physical examination later proved developing pneumonia. It will also be observed from the curves that the lowest vital capacity is usually reached on or near the day of the crisis. From

this time on, if the patient recovers, the vital capacity gradually increases throughout convalescence. In one case of unresolved pneumonia, however (Fig 7), the vital capacity remained almost stationary for a period of ten days following the crisis. In another case in which

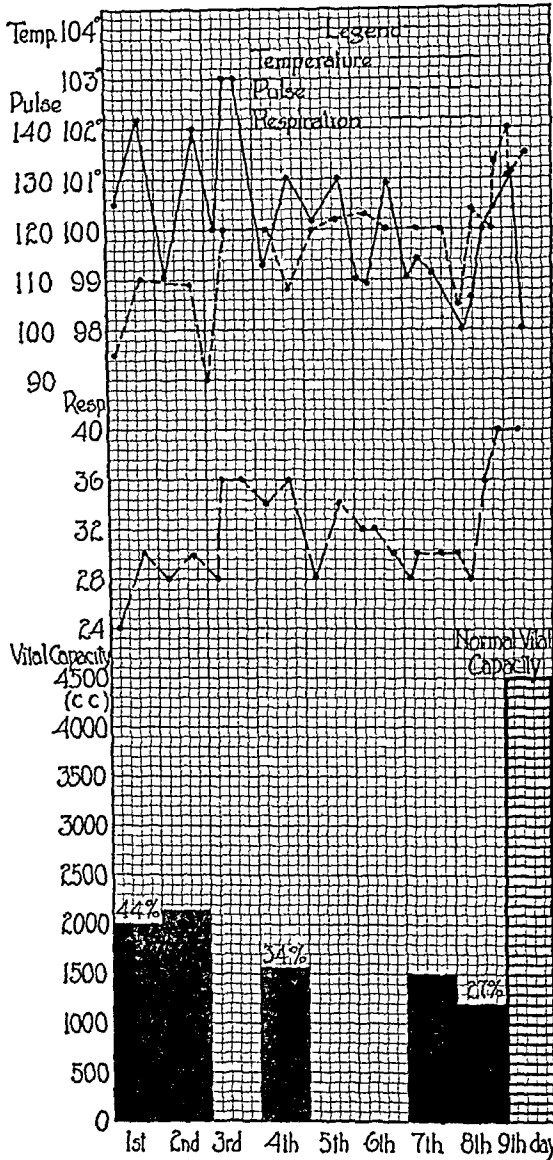


Fig 5—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 47, suffering from broncho-pneumonia with small areas of involvement in all lobes of both lungs. Exodous occurred on the ninth day. On the eighth day of the vital capacity was 27 per cent of the normal.

tubercle bacilli appeared in the sputum during convalescence the vital capacity remained almost unchanged over a long period of time.

In the cases of pneumonia observed, the extent of involvement of lung tissue apparently made very little difference in the reduction of vital capacity, as cases in which physical and roentgen-ray examination

revealed disease limited to a single lobe or a part of one lobe showed a vital capacity as low as was present in cases with much more extensive involvement

In minimal pulmonary tuberculosis, Garvin, Lundsgaard and Van

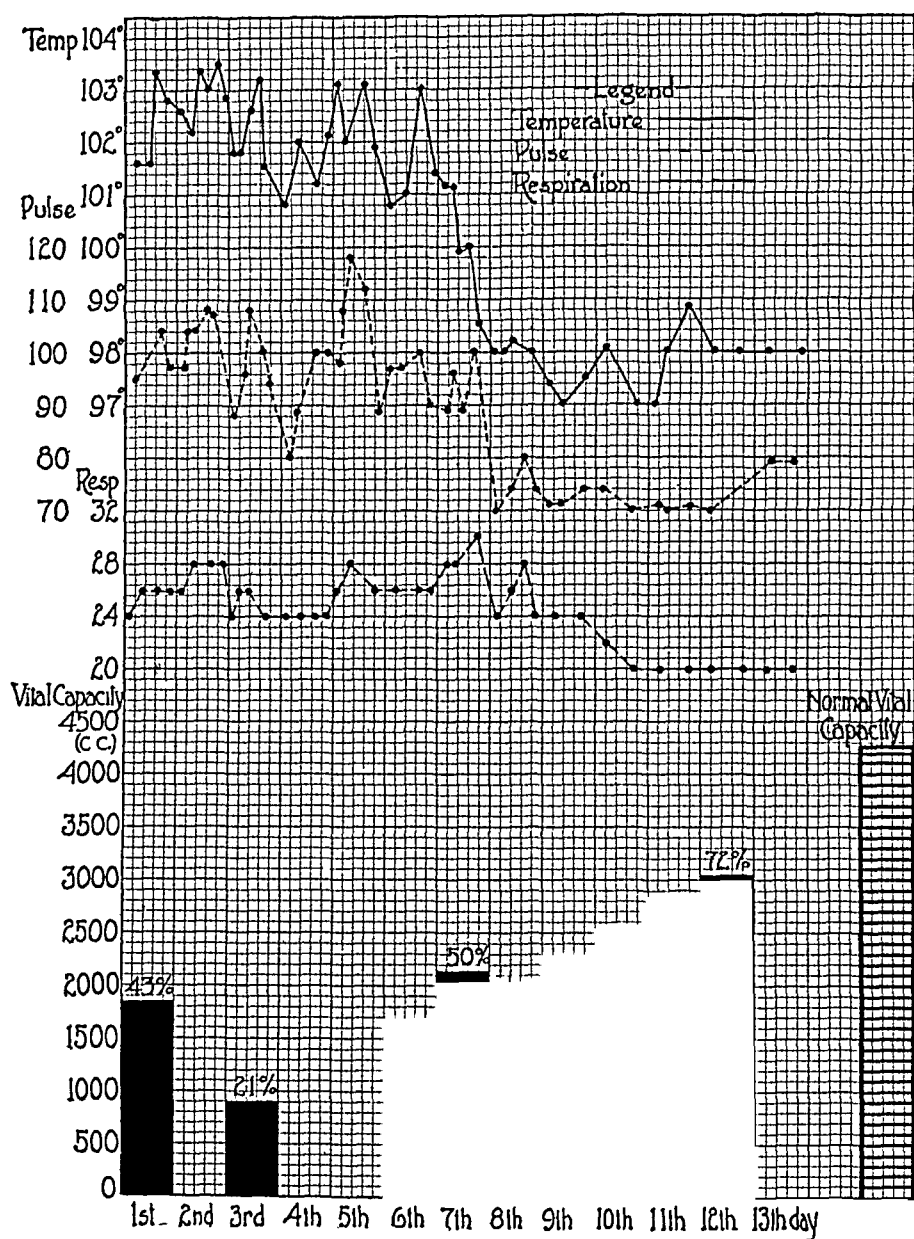


Fig 6—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 40, suffering from lobar pneumonia involving the left lower lobe. Left hospital on the twelfth day with the vital capacity approximately 72 per cent of the normal

Slyke⁹ have shown that the reduction in vital capacity is due to increased residual air, while in the moderately advanced and far advanced stages the reduction is due to a decreased total capacity

⁹ Garvin, A, Lundsgaard, C, and Van Slyke, D. Studies of Lung Volume II Tuberculous Men, J Exper M **27** 87 (Jan) 1918. III Tuberculous Women, J Exper M **27** 129 (Jan) 1918

No attempt was made to ascertain the cause of the reduced vital capacity in pneumonia. Means and Barach¹⁰ call attention to the fact that in pneumonia the extent of the pulmonary consolidation bears no constant relationship to the intensity of the dyspnea. As mentioned above, this is also true as regards vital capacity. Means and Barach

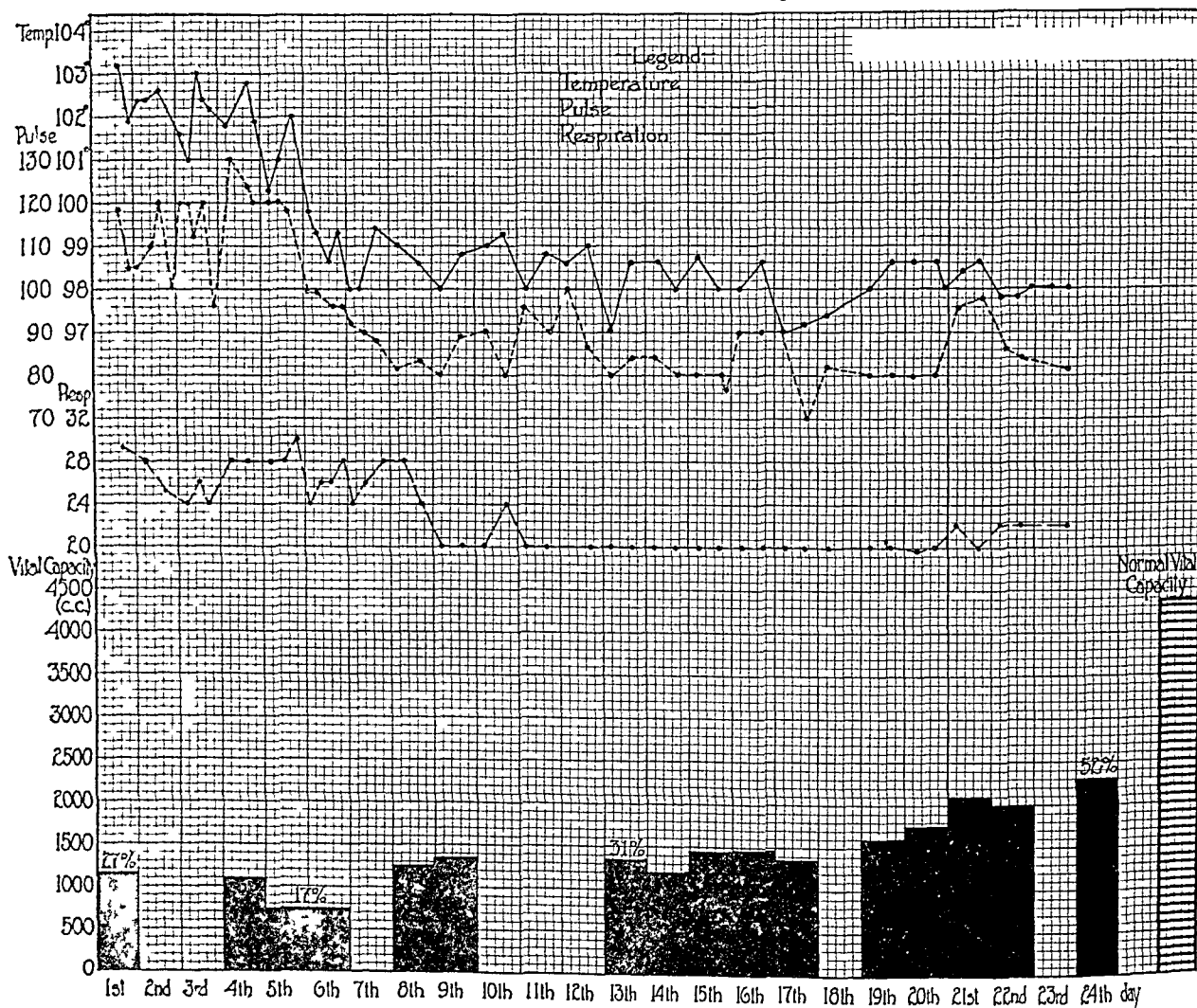


Fig 7—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 23, suffering from lobar pneumonia involving the entire right lung and the upper lobe of the left lung. The lowest vital capacity recorded was 17 per cent of the normal which occurred on the fifth and sixth days. This is a case with delayed resolution. Patient left hospital on the twenty-fourth day with a vital capacity of 52 per cent of the normal.

further point out that dyspnea may cease when the crisis is past with no alteration in the anatomic process in the lungs. This does not hold

¹⁰ Means, J. H., and Barach, A. L. The Symptomatic Treatment of Pneumonia, J. A. M. A. 77:1217 (Oct 15) 1921.

true for vital capacity. Figures 2 to 7 show that the vital capacity is increased almost immediately after the crisis, but does not return to normal for many days.

SUMMARY

1 Observations were made on twenty patients suffering from pneumonia.

2 The lowest vital capacity taken was 17 per cent of the normal. This occurred in one case on the fifth and sixth days of the disease. The highest reading taken was 93 per cent of the normal. This occurred in another case on the day of discharge from the hospital.

3 There was very little relation between the extent of involvement of lung tissue and the reduction of vital capacity.

4 There is probably no other acute disease of the respiratory tract which so reduces the vital capacity from the beginning as pneumonia. Therefore, the vital capacity test is a valuable aid in early diagnosis.

5 During the period of convalescence the vital capacity test offers much information as regards the clearing up of the lesion. An unresolved condition or a complication is indicated by a failure of the vital capacity gradually to increase.

6 The vital capacity is of great value in guiding the patient's activities. Ordinarily patients are discharged from hospitals and allowed to become quite active before their vital capacities have reached a height consistent with such activity. Every patient should remain reasonably inactive in the hospital or the home until the vital capacity has reached at least 90 per cent of the normal.

4 PARATYPHOID FEVER

Peabody and Wentworth⁸ suggested that the reduced vital capacity which is present in patients convalescing from pneumonia may occur in any severe acute infection. Owing to the fact that my observations showed that reduction of vital capacity in pneumonia is not always consistent with the extent of involvement of lung tissue, it was again suggested by several physicians that the high fever and weakness resulting from the toxic condition were responsible for the greater part of the reduction in vital capacity.

Peabody and Sturgis¹¹ studied the effect of general weakness and fatigue on vital capacity. Most of their patients used in the general weakness series were suffering from pernicious anemia, however, one

¹¹ Peabody, F. W., and Sturgis, C. C. Clinical Studies of the Respiration. VIII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, *Arch. Int. Med.* **28**: 501 (Nov.) 1921.

patient had typhoid fever. In none of these cases without heart or lung disease was the vital capacity reduced more than 26 per cent below the normal. In another series of cases an attempt was made to fatigue the muscles of respiration by taking the vital capacity every 15 seconds for 10 minutes. Contrary to what one might expect, the vital capacity was as great at the end of this experiment as at the

TABLE 3—VITAL CAPACITY OF PARATYPHOID FEVER PATIENTS

No	Hospital		Temperature Range	Pulse Range	Respiration Range	Duration of Fever	Vital Capacity				
	Admitted	Discharged					Date Taken	Temperature	Pulse	Respiration	Per Cent
1	3/20/21	5/24/21	97-105	74-140	18-30	22 days	4/ 7/21	103	92	20	64
2	3/16/21	4/15/21	96-104	58- 98	18-22	21 days	3/22/21	103	84	22	65
3	3/18/21	4/20/21	97-105	72-110	18-24	21 days	4/ 4/21	100	82	22	104
4	3/25/21	4/14/21	97-103	60-122	16-25	14 days	3/22/21	99	80	20	68
5	3/19/21	4/18/21	97-104	68-124	18-26	16 days	4/ 7/21	101	88	20	94
6	3/18/21	4/22/21	97-105	60-106	18-24	27 days	4/ 6/21	102	98	22	71
7	3/23/21	3/28/21	96-102	64-100	18-22	3 days	3/22/21	102	100	22	72
8	3/22/21	4/12/21	97-102	54- 96	18-24	14 days	4/ 7/21	99	88	20	91
9	3/21/21	4/21/21	97-104	64-108	18-26	20 days	3/22/21	102	80	20	77
10	3/19/21	4/18/21	97-105	64-128	18-26	28 days	4/ 7/21	99	64	20	75
11	3/29/21	4/12/21	96-104	60-110	16-24	9 days	3/25/21	100	80	18	78
12	3/27/21	4/12/21	97-102	60-108	18-22	10 days	3/25/21	100	90	20	80
13	3/23/21	4/20/21	97-104	64-100	18-26	18 days	4/ 4/21	99	80	20	107
14	3/25/21	4/13/21	97-104	62-104	16-25	16 days	3/22/21	104	92	24	80
15	3/25/21	4/ 5/21	97-103	64-100	16-25	6 days	4/ 7/21	101	84	20	89
16	3/31/21	4/13/21	98-104	60-100	16-22	12 days	3/22/21	105	118	26	89
17	3/24/21	4/ 9/21	97-104	56-114	18-25	12 days	4/ 4/21	102	106	22	90
18	3/21/21	4/ 8/21	97-103	56- 92	16-24	16 days	4/ 4/21	101	96	20	90
19	3/28/21	4/ 8/21	97-101	70- 96	16-22	8 days	4/ 4/21	99	72	18	90
20	3/22/21	4/11/21	97-104	60- 92	16-24	18 days	3/25/21	100	96	22	91
21	3/19/21	5/ 5/21	96-105	70-140	18-26	31 days	4/ 7/21	97	76	20	93
22	4/ 1/21	4/ 7/21	97-100	62- 84	16-20	2 days	4/ 6/21	103	88	20	95
23	3/25/21	4/11/21	97-104	64-106	16-22	15 days	4/ 6/21	98	95	18	96
24	3/23/21	4/21/21	97-104	60-116	18-24	30 days	4/ 6/21	101	88	22	97
25	3/23/21	4/ 8/21	97-103	68-110	18-24	14 days	4/ 6/21	98	88	18	99
26	3/27/21	4/ 5/21	97-100	60- 94	18-20	2 days	4- 6/21	99	84	18	99
27	3/27/21	4/12/21	97-101	60-112	18-22	15 days	4/ 6/21	98	84	20	100
28	3/25/21	4/17/21	97-104	72-116	18-25	20 days	4/ 6/21	101	84	20	101
29	4/ 1/21	4/ 5/21	98-100	62- 84	16-20	2 days	4/ 6/21	101	88	24	102
30	3/27/21	4/ 6/21	96-102	52- 86	16-22	5 days	4/ 7/21	99	96	20	106
31	4/ 1/21	4/17/21	97-103	60-102	16-24	17 days	4/ 6/21	98	90	18	105
32	3/26/21	4/ 9/21	98-102	64-114	16-25	13 days	4/ 6/21	100	80	20	105
								103	90	18	106
								98	86	18	107
								98	94	20	108
								99	84	20	110
								101	98	20	110
								98	80	16	111
								98	84	20	117
								102	88	20	117
								99	80	18	131

beginning. The authors therefore conclude "that general muscular weakness and fatigue of the muscles of respiration are not important factors in causing the reduction of the vital capacity of the lungs in heart disease."

In March and April, 1921, an epidemic of paratyphoid fever occurred at the University of Minnesota which offered an excellent

opportunity to make a study of vital capacity in an acute disease outside the respiratory tract. About sixty cases were placed in the student hospital and it was through the kindness of Professor John Sundwall, director of the Student Health Service, that I was permitted to make observations on these cases. In all cases one reading, and in some cases two readings, were taken. The observations were made while the fever was present or soon after it had subsided. The vital capacity readings were taken with the patients in the reclining position, while the temperature was elevated, and in the sitting posture after the fever had subsided. In most of these cases the vital capacity readings taken at the time the students entered the University of Minnesota were on record in the Department of Physical Education. Inasmuch as some of the students had taken considerable athletic training since their admission to the university their vital capacities had been somewhat increased. In all cases the vital capacity percentage calculations were based on the theoretical vital capacity or the actual vital capacity observed at the time of admission to the university.

Table 3 shows the date of hospital admission and discharge, the temperature, pulse and respiratory range while in the hospital, the duration of fever and the percentage of vital capacity with the temperature, pulse and respiration of each patient at the time the vital capacity readings were taken. In this table the patients are arranged in the order of their vital capacity percentages, beginning with the lowest. Forty-one readings were taken on the thirty-two patients represented in this table. Of these forty-one readings only twelve showed a vital capacity below 90 per cent, the remaining twenty-nine ranged from 90 to 131 per cent.

There were nine cases in which second readings were taken. Five of these showed a vital capacity below 90 per cent on the first examination, but on the second examination the vital capacity had increased to 90 per cent or more. In this series of nine cases there was only one case in which the vital capacity had not increased at the time the second observation was made.

The lowest vital capacity of the entire series was 64.3 per cent. It is interesting to note that before the vital capacity reading was taken this patient developed a rather severe pleurisy which apparently accounted, in part, for the low physical fitness percentage.

In Case 2 the vital capacity percentage was only 65.4 at the time of the first reading. About twenty-four hours later, the internist, with no knowledge of the results of the vital capacity test, recorded the presence of a slight cardiac disturbance believed to be due to toxemia. All signs of this disturbance disappeared in a few days and about two weeks from the time of the first reading the vital capacity was found to

be 104 per cent. It will be recalled that Peabody and Wentworth⁸ and Nathanson and Ulrich¹² and others¹³ have reported marked reduction in vital capacity due to true cardiac lesions.

At the outbreak of this epidemic all cases with similar symptoms were placed in the same wards. The vital capacity test was taken in most cases before a diagnosis was recorded. Three cases were found in which the vital capacity was reduced 50 per cent or more. It is interesting to note that each of these patients was developing pneumonia, which later was revealed by physical examination.

In the remaining seven cases in which the vital capacity was reduced to below 90 per cent of the normal, I have no explanation for the reduction unless it is due to toxemia. Unfortunately, however, these patients were not sent to the department of roentgenology nor were electrocardiographic studies made to find evidence of the presence or absence of deeply seated pulmonary lesions or the existence of heart lesions otherwise undiscovered.

Inasmuch as some of these cases at no time showed severe toxic manifestations, one hardly seems justified in trying to account for the reduction in lung capacity on the basis of toxemia.

It is interesting to note that in some of the remaining cases in which vital capacities were found to be within normal limits, the temperature ranged as high as 105 F, and the pulse ranged as high as 140 per minute.

SUMMARY

1 Observations were made on sixty patients suffering from paratyphoid fever.

2 Fifteen per cent of these cases had vital capacities below normal limits. In more than 50 per cent of these cases with reduced vital capacities, however, the reduction was explained on the basis of such complications as pleurisy or lung involvement.

3 In 85 per cent of the cases the vital capacity was within normal limits.

4 In this study the vital capacity test was found to be valuable in suggesting beginning complications such as pleurisy and pneumonia.

12 Nathanson, M. H. and Ulrich, H. L. The Vital Capacity of the Lungs in Cardiac Disease, *Minnesota Med* **4** 721 (Dec.) 1921.

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THE EFFECT OF THE ADMINISTRATION OF HYPERTONIC SALT SOLUTION ON THE BLOOD VOLUME AND CERTAIN RELATED BLOOD CONSTITUENTS

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INTRODUCTION

Weed and McKibben¹ demonstrated that the intravenous administration of hypertonic salt solution to animals was attended by a decrease in the size of the brain and a fall in cerebrospinal pressure. These results were soon applied to patients by Cushing and Foley,² Sachs and Belcher³ and others.⁴ The usual intravenous dose was 100 c.c. 15 per cent sodium chlorid solution (in some instances 30 per cent). As a result of these injections cerebral hemiae often disappeared or were much diminished, the swollen brain decreased in size so that operations on it could be performed more easily, and the elevated cerebrospinal pressure of patients with brain tumor was usually reduced promptly. The effects were, in general, so satisfactory that the adoption of intravenous hypertonic salt solution as a valuable therapeutic measure appeared likely. With these facts in mind, it seemed to us desirable to ascertain what alterations took place in the blood as a result of its use, and especially the degree and significance of these alterations. The various factors investigated were the blood volume, blood chlorids, the relation between blood volume and blood chlorids, the effects produced on the red corpuscles and hemoglobin, and the oxygen and carbon dioxide content of venous blood. We regret that a greater series was not obtained for each factor, but this would

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1 Weed, L. H. and McKibben, P. S. *Am. J. Physiol.* **48**: 512, 1919.

2 Cushing, H., and Foley, F. B. *Proc. Soc. Exper. Biol. & Med.* **17**: 217, 1920.

3 Sachs, E., and Belcher, G. W. *J. A. M. A.* **75**: 667 (Sept. 4) 1920.

4 Cobb, S., and Aver, J. B. At the Massachusetts General Hospital. Personal communication.

have necessitated the withdrawal of an inconveniently large amount of blood. Since the procedure was relatively new and untried, it was undertaken only in the case of patients whose condition definitely indicated its use, a fact which further limited the series obtained. The intravenous human dosage was 100 c c of 15 per cent sodium chlorid solution. The animals received a corresponding or relatively larger dose. Hypertonic salt solution was administered intravenously to seven patients, by mouth to one patient and one normal person and intravenously and by mouth to eight rabbits.

HISTORICAL

Blood hydremia has been observed in animals following the intravenous administration of hypertonic solutions by Brasol,⁵ Kilkowitz,⁶ Magnus⁷ and others. Magnus demonstrated the hydremia following hypertonic salt solution by reduction in the hemoglobin percentage, the specific gravity and dried ash of the blood. No measurements of the absolute changes in plasma volume after hypertonic salt administration have been encountered. Other effects observed in animals have been a prompt diuresis, a depression of the freezing point of the serum,⁷ a hyperglycemia and glycosuria,⁸ and occasional fever.⁹ Magnus⁷ found that the increase in chlorids in the blood after the injection was apparently less than the chlorids introduced.

Hypertonic salt solution was first administered intravenously to patients by Velden¹⁰ in 1909. Beginning with 5 c c of a 10 per cent solution, he gradually increased the dose to 100 c c. He discovered that a striking acceleration of the coagulation time of the blood took place, and used it with good results in cases of hemorrhage.¹¹ The diminished coagulation time after hypertonic sodium chlorid solution has been confirmed and has been shown to occur after the intravenous administration of other hypertonic salt solutions, as calcium chlorid¹² and sodium citrate.¹³ It also occurs after the oral administration of sodium chlorid.¹⁴ It has been supposed that some coagulation furthering substance present in tissue juice is drawn into the blood along with the

5 Brasol, L. Arch f Anat u Physiol S 210, 1884

6 Kilkowitz, S. Arch f Anat u Physiol S 518, 1886

7 Magnus, R. Arch f Exper Path **44** 68, 1900

8 Hirsch, E. Ztschr f physiol Chem **94** 227, 1915

9 Rolly, F, and Christjanson, A. Arch f exper Path u Pharmakol **77** 34, 1914

10 Van der Velden, R. Deutsch med Wchnschr **35** 197, 1909

11 Van der Velden, R. Zentralbl f Herz u Gefasskrankh **11** 61 (March) 1919

12 Schenk, P. Ztschr f d ges exper Med **11** 166, 1920

13 Blumel. Med Klin, 1910

14 Neuhof, H, and Hirshfeld, S. New York M J **133** 95 (Jan 15) 1921

tissue fluid In man a hypoglycemia without glycosuria has been observed after the injection, in contrast to the hyperglycemia found in rabbits ¹⁵

It has recently been reported that the administration of hypertonic solutions produces a general inhibition of glandular secretions, including sputum, sweat, gastric juice, milk, bile and the thyroid secretion ¹⁶ For these effects 50 per cent dextrose solution was generally used in preference to hypertonic salt solution The clinical results may be mentioned briefly Night sweats have been diminished, gastric hyperacidity has been controlled, with relief of symptoms, and profuse expectoration associated with suppurative bronchitis, asthma, tuberculosis or pulmonary edema generally has been much decreased after the employment of these hypertonic solutions ¹⁷ Profuse choleraic diarrhea and severe toxic dysenteries have been suppressed in like manner In fourteen out of fifteen cases of hyperthyroidism and pronounced exophthalmic goiter, Stejskal ¹⁶ observed distinct diminution in the size of the thyroid after the injection of hypertonic solutions, with marked improvement in the symptoms and signs of the disease Two of his patients continued to work two and three months, respectively, after treatment without evidence of symptoms The glandular inhibition presumably arises because the tissue lavage into the blood diminishes the supply of fluid to the glands It has been claimed also that there is an accelerated absorption of drugs introduced into the body, as sodium iodid by mouth, cocain applied to the mucous surfaces, and arsphenamin intravenously ¹⁶

Wynn ¹⁸ tried the effect of hypertonic salt in the treatment of neurosyphilis, since it has been shown that with the fall in cerebrospinal pressure a considerable amount of subarachnoid fluid entered the substance of the central nervous system ¹⁹ He gave 200 c c of 15 per cent sodium chlorid solution intravenously in the hour following intraspinal injection, but found no serologic or cytologic improvement over the usual course of intraspinal treatment Corbus ²⁰ and his co-workers used hypertonic salt as a method of spinal drainage, having shown that six hours after the injection there was a reabsorption of serum from the blood stream into the cerebrospinal fluid which carried the arsphenamin introduced intravenously into the spinal canal

Burger and Hageman ²¹ recommend 50 per cent sugar solution (grape sugar) in doses of 1 gm dextrose per kilo body weight They

15 Schenk, P. *Ztschr f d ges exper Med* **12** 269, 1921

16 Stejskal K. *Wien klin Wchnschr* **34** 200, 343, 1921

17 Singer, G. *Wien klin Wchnschr* **34** 86, 1921

18 Wynn, J. *Arch Int Med* **29** 72 (Jan) 1922

19 Foley, F B and Putnam, T J. *Am J Physiol* **53** 464, 1920

20 Corbus, B C, O'Connor, V J, Lincoln, M C, and Gardner, S M
J A M A **79** 264 (July) 1922

21 Burger M, and Hageman E. *Deutsch med Wchnschr* **47** 207, 1921

are now applying it to cases of lumbago and sciatica. In this country favorable results following hypertonic sugar solutions have been reported in influenzal pneumonia,²² in other severe infectious diseases,²³ in traumatic shock,²⁴ and in glaucoma.²⁵ Such a varied usage of this relatively new therapeutic measure would seem to offer a wide field for future clinical research. In this report, in addition to the effect on the composition of the blood, the clinical results in the patients with increased cerebrospinal pressure will be mentioned.

METHODS

Absolute changes in blood volume were determined by the vital red method of Keith, Rowntree and Geraghty,²⁶ the principle of which depends on the color dilution of a known amount of dye when circulated in the blood stream. A sample of blood is first drawn, the dye is injected and allowed to circulate for three minutes for thorough mixing of dye and blood, and a second blood sample is withdrawn. The color dilution of the dye in the plasma gives a quantitative determination of the plasma volume, from which with the hematocrit, the total blood volume can be calculated. By utilizing the fact that no appreciable amount of the dye is excreted in the first ten minutes, it was possible to make a second determination of the blood volume within this period. The hypertonic salt solution was injected and a third blood sample was removed within this interval. Two readings were thus made on the identical quantity of dye injected, which served as an accurate control and in addition allowed the measurement of blood changes taking place immediately after the injection. Other methods of recording absolute blood changes are more time consuming and apt to result in a merging of the early swift changes in plasma volume. A third determination with this method is not possible for twenty-four hours, or until all traces of the dye have left the blood stream. Six satisfactory determinations were made in this manner in Case 1 (Table 1).

Relative changes in blood volume were determined by changes in hemoglobin content, the red blood cell count, and the hematocrit percentage. The formula used was that of Boycott and Douglas,²⁷ and may be illustrated as follows:

$$\frac{120\% \text{ (hemoglobin before)}}{80\% \text{ (hemoglobin after)}} \times 100 = 150 \text{ per cent, or the blood}$$

22 Wells, C W, and Blankinship, R C. *J A M A* **74** 75 (Jan 10) 1920

23 Litchfield, L. *J A M A* **71** 503 (Aug 17) 1918

24 Erlanger, J. *J A M A* **69** 1410 (Oct 27) 1917

25 Sansum, W D. *J A M A* **68** 1885 (June 23) 1917

26 Keith, N M, Rowntree, L G, and Geraghty, I T. *Arch Int Med* **16** 547 (Oct) 1915

27 Boycott, A E, and Douglas, C J. *J Path & Bacteriol* **13** 256, 1909, *ibid* **16** 485, 1912

volume after saline injection in per cent of the normal or original blood volume

This method depends on the assumption that the volume of circulating hemoglobin is constant under control conditions. It is known that the red corpuscle content of the blood is altered by a number of conditions, among them low oxygen tension,²⁸ fright,²⁹ exercise, sweating, administration of epinephrin, abdominal massage,³⁰ and also that it varies at different periods of the day.³¹ Consequently, the calculation of the blood volume changes for any length of time on the basis of variations in red cell or hemoglobin percentages would seem to be fraught with error. Bogert, Underhill and Mendel,³² however, found that the hemoglobin of rabbits did not vary appreciably for a period of several hours. In Case 1 of this series comparisons were made between the blood volume changes as determined by vital red method and the relative changes as determined by dilution of hemoglobin, red corpuscles and hematocrit. The immediate changes following the infusion were quite comparable, but at the end of twenty-four hours a discrepancy occurred. It seems probable that for short periods of time relative blood volume changes can be determined fairly by methods that depend on hemoglobin dilution, but for periods as long as twenty-four hours an error may be introduced.

The analyses of the blood oxygen and carbon dioxide were done by the method of Van Slyke and Stadie.³³ The hemoglobin was calculated from the oxygen capacity. The chloride determinations were carried out by the method of Wetmore.³⁴ Except when the oxygen and carbon dioxide contents were determined, the blood was not withdrawn under oil. The influence of a diminishing tension of carbon dioxide on the distribution of chlorides between plasma and red corpuscles would make our figures for the plasma chlorides a little high.³⁵ For this reason no precise comparisons of the exchange of chlorides between plasma and cells following injection of hypertonic salt solution have been made.

In the case of rabbits the salt solution was injected into the ear vein, and the blood withdrawn from the heart. In the patients, the brachial veins were used.

28 Fitzgerald. Quoted from Haldane, J. S. *Organism and Environment* 1917, p. 52.

29 Lamson, J. *J. Pharmacol. & Exper. Therap.* 7: 169, 1915.

30 Schneider, E. C., and Havens, L. C. *Am. J. Physiol.* 36: 239, 1915.

31 Dreyer, G., Bazett, H. C., and Pierce, H. F. *Lancet* 1: 588, 1920.

32 Bogert, L. J., Underhill, F. P., and Mendel, L. B. *Am. J. Physiol.* 41: 189, 1916.

33 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* 49: 1, 1912.

34 Wetmore, A. S. *J. Biol. Chem.* 45: 113, 1920.

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Fridericia, L. S. *J. Biol. Chem.* 42: 245, 1920.

DISCUSSION OF RESULTS

Blood Volume—The most striking result of the intravenous injection of hypertonic saline solution was an immediate and marked increase in the plasma volume. The administration of 100 cc of 15 per cent sodium chlorid solution was followed within one or two minutes after the injection by an elevation of from 15 to 30 per cent of the total blood volume, representing a pouring into the blood stream of from 500 to 1,200 cc of tissue fluid. The greatest increase in blood volume was noted approximately thirty seconds after the injection, i. e., as soon after as the blood could conveniently be drawn. From then on it progressively diminished, and in most cases returned nearly to the original volume within three and one-half hours. In one case in which the plasma volume was abnormally lowered before the injection, the increased blood volume persisted for four days. The factors that govern the magnitude, the time relationship, and the relative permanency of the changes in plasma volume may be grouped as follows: (1) the total increase in chlorids present in the entire circulating blood at the time of the analysis, (2) the condition of the kidneys. Other factors, such as the amount and concentration of the solution, the speed of injection, the weight of the subject, and the amount of chlorids in the body, may be considered subdivisions of the first group. In order to show how these factors explain the mechanism of the elevation in blood volume, the chlorid content of the entire blood was determined before and after the injection of hypertonic salt solution. The total increase in sodium chlorid was then compared to the increase in blood volume. It was found the volume response was essentially that which would fulfil the isotonic requirements of the increased salt. In other words, the normal isotonic concentration of the blood was in the main preserved. The detailed calculations follow.

The chlorid content of the entire circulating blood may be determined by multiplying the absolute blood volume by the chlorid concentration in grams per liter of whole blood. Similarly, the chlorid content of the entire plasma is determined by multiplying the plasma volume by the plasma chlorid concentration. The difference between these two figures gives the chlorid content of the entire red cells. With the hematocrit the chlorid concentration of red corpuscles in grams per liter can be calculated (Table 1). If, in case 1, these figures are charted graphically together with the blood and plasma volume after the intravenous administration of hypertonic salt solution, a close parallelism is found between the blood and plasma volume, on the one hand, and the total quantity of chlorid in the circulating blood or plasma on the other. Slight discrepancies exist which will be discussed later. Between the blood volume and the chlorid concentration in grams per liter of whole blood or plasma an approximate parallelism is present. In the other

TABLE 1.—BLOOD ATTRACTIONS FOLLOWING INTRAVENOUS ADMINISTRATION OF HYPERTONIC SALT SOLUTION THE RELATION BETWEEN THE INCREASE IN BLOOD VOLUME AND THE INCREASE IN TOTAL CHLORIDS

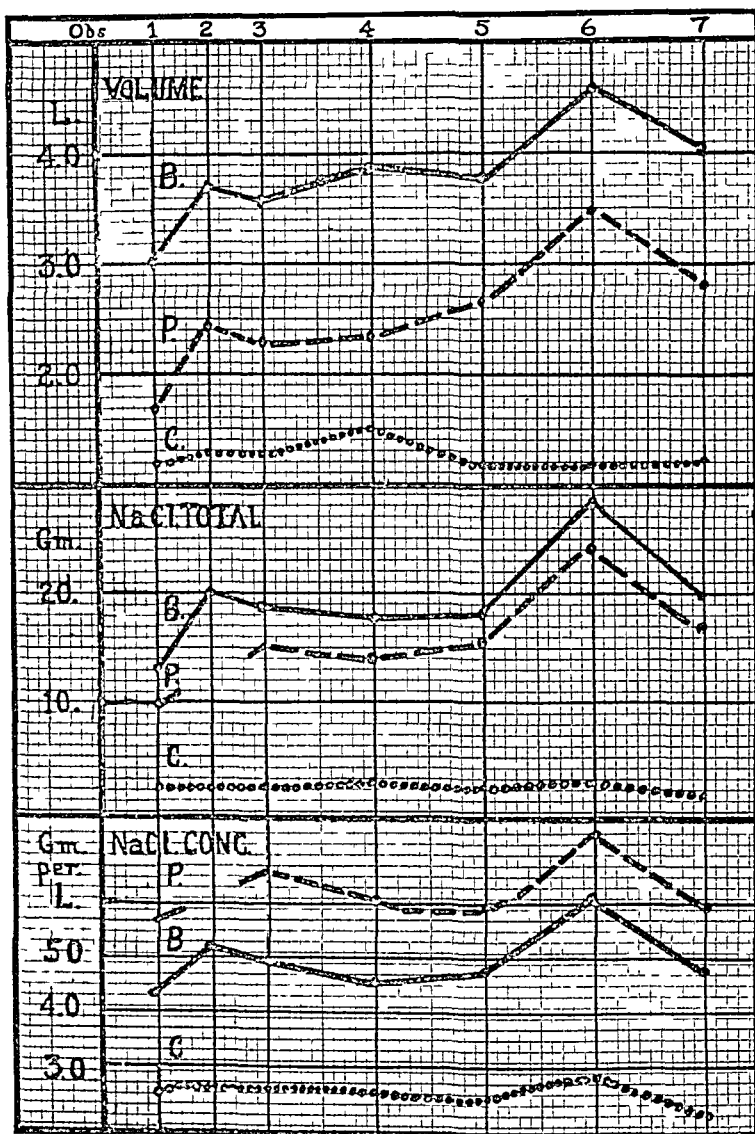
Case No., Age, and Diagnosis	Date	Time of Observation (Note Fresh injection = 15 gm NaCl in 100 c.c. of Water)	Hemo- globin (Calcu- lated from Oxygen Capac- ity), per Cent	Red Blood Cells, per O Mm	Hema- to- crit Cells, per Cent.	Blood Volume Data			Blood Chlorid Data						Comparison of Volume and Chlorid Data		Remarks	
						Total Blood, O c	Total Plasma, O c	Total Cells, O c	Concentra- tion in			Total in Circulating			Total Increase in Chlorids of Entire Blood, O Gm	Actual Increase in Blood Vol- ume		Volume Theo- retically Necessary to Render Increased Chlorids Isotonic, O/O 9
									Whole Blood, Gm per Liter	Plasma, Gm per Liter	Cells B, Gm per Liter	Blood, Gm	Plasma, Gm	Cells, Gm				
1	5/26	Before 1st injection	104.5	4,136,000	41.6	2,979	1,739	1,240	4.38	5.68	2.55	13.07	9.88	3.19	6.78	761	774	Stupor and inar- tulate, twitching of hands
26 years, Cyst of the cerebellum		2 min after injection (duration of injec- tion, 3 min)	82.7	3,421,000	31.6	3,740	2,445	1,295	5.31			19.85			6.78	761	774	Brighter, slurring speech present
		1 hr after injection	83.3	3,480,000	36.0	3,618*	2,315	1,303	5.11	6.57	2.53	18.47	15.40	3.07	5.10	639	601	
	5/27	24 hrs after injection	90.6	3,480,000	39.0	3,880	2,363	1,517	4.60	6.01	2.41	17.85	14.20	3.65	4.78	901	532	Twitching of hands continues
	5/31	Before 2d injection	90.4	3,536,000	31.0	3,781	2,606	1,175	4.82	6.02	2.16	18.24	15.70	2.54			1173	
		1/2 min after injec- tion (duration of injection 1 min)	80.4	3,192,000	25.0	4,675	3,508	1,167	6.16	7.29	2.76	28.80	25.59	3.21	10.56	894		Brighter, less twitching
		3 1/2 hours after injec- tion	88.2	3,300,000	31.0				5.35	6.08	2.38							
	6/1	Before 3d injection (24 hrs after 2d injection)	86.2	3,328,000	30.8	4,675	2,819	1,256	4.85	6.17	1.88	19.77	17.38	2.39	1.53	294	170	Twitching again
		10 min after injec- tion (duration of injection, 7 min)	72.7	2,840,000	25.0					6.82								Unchanged
		3 hrs after injection	83.3	3,392,000	30.6				5.28	6.30	2.97							Brighter and stronger
	6/6	5 days after injection	91.7		28.6				4.54	5.46	2.27							Carpopedal spasm

* In this instance, the blood volume was calculated from the previous vital red determination and the relative difference in hematocrit. In all others the vital red method was used directly.

TABLE 2—BLOOD ALTERATIONS FOLLOWING HYPERTONIC SALT SOLUTION

Case No., Age, and Diagnosis	Administration of Hypotonic Salt				Hemo- globin Calcu- lated from Oxygen Capac- ity, per Cent	Red Blood Cells		Hema- toerit Red Cells, per Cent	NaCl Concentration			Venous Blood			Blood Volume Calculated from		Fragility of Red Blood Cells	Remarks								
	Amount	Dura- tion	Avenue	Time of Observa- tion		Capillary Blood, per C Mm	Venous Blood, per C Mm		Whole Blood, Gm per Liter	Plasma A, Gm per Liter	Red Cells B, Gm per Liter	Oxy- gen Con- tent, Vol per Cent	Oxy- gen Satu- ration, per Cent	Carbon Dioxid Con- tent, Vol per Cent	Hema- toerit, per Cent	Hemo- globin, per Cent										
2 35 years Tumor of cerebellum	100 c c 15% NaCl	5 min	Intra- venous	Before	4,256,000		35.3	4.72	6.31	1.81	15.83	76.5	51.0	100	100	Hemolysis 42-34, cells gone at 26 Hemolysis 38-32, cells gone at 24 Hemolysis 42-34, cells gone at 28	Marked stupor									
				3 min after														26.6	6.08	8.08	2.82	10.15	63.1	54.0	133	128
				24 hrs after																						
3 40 years Tumor of cerebellum	100 c c 15% NaCl	8 min	Intra- venous	Before			41.4	4.74	5.77	2.56	9.03	42.0	60.3	100	100	Control cells plus plasma dilution, hemolysis 36-24 Control cells plus plasma dilution, hemolysis 36-24	Stuporous									
				12 min after														36.6	5.03	7.29	1.12	6.93	40.2	60.8	113	125
4 22 years Fracture Of skull	100 c c 1500% Ringer's solu- tion	5 min	Intra- venous	Before	5,228,000	5,184,000	46.7	4.51	5.93	2.89	15.43	66.9	61.3	100	100		Serum clear									
				2 min after														42.0	4.83	6.33	2.76	14.43	65.3	57.0	111	104
				20 hrs after																						
5 26 years Normal	50 c c 15% NaCl	7 min	By mouth	Before	4,928,000		43.4	4.80	6.11	3.09	11.95	56.0	56.7	100	100	One hour after lunch										
				15 min after													43.0	4.89	6.33	6.93	11.24	50.5	54.5	101	100	
				1½ hrs after																						42.7

human cases, as well as in the experiments on rabbits, an approximate parallelism between the relative blood volume after the administration of hypertonic salt solution and the chlorid concentration of whole blood or plasma is also present (Tables 1, 2 and 4) The chlorid concentration in the red corpuscles and the chlorid content of the entire red blood cells show no constant relationship to the blood volume



Relation between blood volume and blood chlorids following the intravenous administration of hypertonic salt solution. Results obtained in Case 1. B, whole blood, P, plasma, C, cells. The upper group shows the total blood, plasma and cell volume, expressed in liters (L), the middle group, the total sodium chlorid in whole blood, plasma and cells, expressed in grams, the lower group, the concentration of sodium chlorid in whole blood, plasma and cells, expressed in grams per liter.

Observation (Obs) 1 was made just before an injection of 100 cc of 15 per cent sodium chlorid. Obs 2, two minutes after, Obs 3, one hour after, Obs 4, twenty-four hours after, Obs 5, one hundred hours after and just before the second injection, Obs 6, thirty seconds after the second injection, Obs 7, twenty-four hours after the second injection.

It thus appears from the chart that the increase in total chlorids of either blood or plasma is proportional to the volume increase in either blood or plasma. It may be mentioned at this point that the increase in blood volume after hypertonic salt injection is due almost entirely to the increase in the plasma volume. An exception to this occurred in Case 1, twenty-four hours after the first injection, when apparently a considerable increase in cell volume took place. For the most part, however, the blood volume reflects the changes in the plasma volume. A more accurate basis for comparing the blood volume and the blood chlorids may be had by calculating the number of cubic centimeter of water theoretically necessary to bring the increased chlorids in the blood into an isotonic state. This is done simply by dividing the total chlorid increase in grams by 0.9. If this number, conveniently called the isotonic equivalent of the chlorid increase, is compared to the actual increase in blood volume reckoned in cubic centimeter, it is found that at times they are approximately equal to each other, and at other times there is a certain divergence (Table 1). When the actual increase in blood volume after injection of hypertonic salt solution is equal to the isotonic equivalent of the chlorid increase, it is evident that the blood remains isotonic. When the actual increase in volume is less than the number of cubic centimeter of water necessary to bring the increase in chlorids to isotonicity (less than the isotonic equivalent), the blood is obviously to some extent hypertonic, provided other conditions remain constant. Thus, in Case 1, after the first injection the increase in chlorid content of the entire blood was 6.78 gm, its isotonic equivalent was 7.54 c.c., and the recorded increase in blood volume 7.61 c.c. In this instance it would appear that the increase in blood volume was the amount necessary to bring the chlorid increase in the blood into an isotonic state, and consequently that the osmotic pressure of the blood remained approximately as it was before the injection, i.e., equal to a solution of sodium chlorid of a concentration of 0.9 per cent.

If the immediate changes after the second injection are now examined, the chlorid increase is seen to be 10.56 gm, its isotonic equivalent 11.73 c.c., and the recorded increase in blood volume 8.94 c.c. In this case, 2.79 c.c. of fluid are theoretically still needed to bring the chlorid increase to an isotonic state. The blood would thus appear to be hypertonic, containing a total excess of 2.51 gm of chlorid above the physiologic concentration, or 0.537 gm per liter.

The provision was made in these calculations concerning the isotonicity of the blood that the other factors involved remained constant. The other factors involved in maintaining the osmotic pressure of the blood do not, however, remain constant, but undergo marked changes. Their alterations complicate but at the same time strengthen the conclusions drawn.

Assuming that the osmotic pressure of the blood before the second injection was equal to that of physiologic solution of sodium chlorid, 0.9 per cent, the part played by the chlorids in the blood in maintaining the osmotic pressure is equivalent to 0.482 per cent (The chlorid concentration of whole blood before the second injection was 4.82 gm per liter). There are, thus, 0.418 per cent (of the osmotic pressure of the blood in terms of physiologic sodium chlorid solution) to be furnished by other substances, such as glucose, sodium bicarbonate, other salts, and colloids. After the second injection, the chlorid concentration of whole blood was 6.16 gm per liter, an increase of 1.34 gm per liter. It would appear at first glance that each liter of blood was hypertonic to the extent of 1.34 gm per liter, whereas in the previous calculations from the increase in blood volume, the hypertonicity was estimated at 0.537 gm per liter. The difference between the two, 0.803 gm per liter, does not, however, represent additional hypertonicity, but takes the place of the osmotic substances other than chlorids that are lost from each liter of blood by dilution with tissue fluid. Thus, after the injection, 894 c.c. of new fluid was found in the blood stream. The substances making up the 0.418 per cent of the osmotic pressure (glucose, sodium bicarbonate, etc.) of necessity spread equally throughout the new blood volume and become correspondingly diminished in each liter of blood, so that the concentration of these substances became 0.338 per cent, or a loss of 0.80 gm per liter. This is equal to the discrepancy noted above, and represents a replacement by chlorid of the osmotic substances lost by dilution. The concentration of these substances after the injection, 0.338 per cent, plus the chlorid concentration after the injection, 0.616 per cent, equals 0.954 per cent, representing a hypertonicity equivalent to 0.54 gm per liter, which corroborates the original calculation of 0.537 gm per liter (0.338 per cent, or the concentration of the other osmotic substances in terms of sodium chlorid after salt injection, is derived as follows: $0.418 \text{ per cent [concentration of substances before injection]} \times 3781 \text{ [blood volume before]} - 4675 \text{ [blood volume after]} = 0.338 \text{ per cent}$).

Similar calculations applied to the results immediately after the first injection indicate that the blood was practically isotonic in this instance, corroborating the agreement between the isotonic equivalent of the chlorid increase and the actual increase in blood volume.

Twenty-four hours after the first injection, the actual increase in blood volume appears somewhat greater than the isotonic equivalent of the sodium chlorid increase. Thus, the sodium chlorid increase of the entire blood was 4.78 gm; its isotonic equivalent 532 c.c., the actual increase in blood volume 901 c.c. It must be remembered, however,

that the osmotic substances other than sodium chlorid which become diluted through the ingress of tissue fluid probably revert to their original concentration after twenty-four hours, and restore the osmotic substances lost by dilution. If this calculation is carried out on that basis, the blood concentration is practically isotonic. Similarly, the increase in blood volume twenty-four hours after the second injection is in excess of the isotonic equivalent, but that excess is again equivalent to the osmotic substances that presumably enter the blood from the tissues to maintain the original concentration. The calculation on this basis again yields a practically isotonic concentration. (Thus, 0.485 per cent [concentration of osmotic substances before second injection] + 0.418 per cent [chlorid concentration after injection] = 0.903 per cent.)

It would appear from these results that the total increase in chlorids present in the circulating blood at the time of analysis is the primary determinant of the blood volume following hypertonic salt solution injection. The amount of increase of the blood volume corresponds approximately to the amount of fluid necessary to render the increased chlorids isotonic.

The discrepancies, which occur twenty-four hours following the injection, have been explained above. Thirty seconds after the second injection, the blood was apparently to some degree hypertonic, inasmuch as the increase in blood volume did not fully meet the requirements for isotonicity. Thorough mixing of blood and chlorides was probably not established, so that this may not have represented the condition throughout the entire body. It will be remembered that a depression of the freezing point of the serum after hypertonic salt has been demonstrated in animals, but in these investigations the amount of salt injected was relatively much larger.

The second important factor in determining the permanency of the increased blood volume appears to be the condition of the kidneys. Boycott and Douglas³⁶ showed that after the injection in rabbits of a quantity of physiologic solution of sodium chlorid equal to the calculated blood volume, the original blood volume returned to normal within thirty minutes. Two thirds of the injected quantity left the circulation during the administration, the duration of which was five minutes. This occurs with both ureters ligated, but in rabbits in whom uranium nephritis had been produced, the blood volume failed to return to normal in the allotted time. When double strength Ringer's solution was injected, only one third of the injected amount left the circulation in the first five minutes. White and Erlanger³⁷ found that

36 Boycott, A. E., and Douglas, C. J. *J. Path. & Bacteriol.* **19** 221, 1914.

37 White, H. L., and Erlanger, J. *Am. J. Physiol.* **54** 1, 1920.

in dogs a strongly hypertonic solution of glucose and gum acacia solution caused a marked increase in relative blood volume which gradually fell but did not return to normal in several hours. Magnus⁷ studied the diuresis taking place in rabbits after the intravenous administration of salt solutions of varying concentrations, and found the degree of diuresis ran parallel to the degree of blood dilution. Galeotti³⁸ found that the diuresis varied inversely as the molecular concentration of the blood. The urinary output could not be followed in the present study as most of the patients were incontinent. None of the patients had

TABLE 3—RELATIVE BLOOD VOLUME FOLLOWING HYPERTONIC SALT SOLUTION

Case No., Diagnosis and Age	Administration of Salt Solution				Hema- toerit Cells, %	Blood Volume Calcu- lated from Hema- toerit, %	Remarks
	Amount	Dura- tion	Avenue	Time of Observa- tion			
6 Brain tumor? 30 years	100 c c 15% NaCl	5 min	Intra- venous	Before 1 min after 2 min after 30 min after 1½ hrs after 24 hrs after	47.2 36.9 36.8 39.3 39.0 41.2	100 128 128 120 121 114	Sleepy, severe headache Felt very hot Headache gone No longer sleepy Patient brighter, no headache
7 Brain tumor 28 years	100 c c 15% NaCl	7 min	Intra- venous	Before ½ min after 1 min after 3 min after 3 hrs after	46.0 39.1 42.5 44.0 44.0	100 118 108 105 105	Slight headache Face felt hot Headache gone
8 Brain tumor 29 years	100 c c 15% NaCl	12 min	Intra- venous	Before 1 min after 3 min after 10 min after 22 min after 40 min after	46.4 40.3 41.8 43.8 44.1 44.6	100 115 111 106 105 104	Headache Felt very hot Headache gone, no complaints
9 Polycy- themia vera 55 years	100 c c 10% NaCl	3 min	By stom- ach tube	Before 15 min after 30 min after 1 hr after 1½ hrs after	72.0 69.0 68.4 67.5 67.8	100 104 105 107 106	

demonstrable nephritis. In some of the rabbits, however, chlorid retention was present in the blood, shown by the immediate increase in blood chlorids failing to drop to normal subsequently. In these rabbits there was a parallel maintenance of the increased blood volume. Instances of the normal reaction in rabbits, an abrupt rise in blood volume immediately after the injection followed by a gradual fall, may be seen in experiments 1 and 3 (Table 5). In experiments 5, 6, 7 and 8 (Table 4) the relative blood volume showed an immediate increase which either remained stationary or became further elevated, and the chloride concentration of the blood and plasma likewise remained elevated. It is to be remembered that the chlorids of the entire blood were

TABLE 4—BLOOD CHLORIDS AND RELATIVE BLOOD VOLUME IN RABBITS FOLLOWING HYPERTONIC SALT SOLUTION

Experi- ment Number and Weight of Rabbit	Administration of 15% Salt Solution				Hemato- crit Red Cells, %	Red Blood Cells (Venous Blood), per O Mm	Blood Volume Calculated from		Blood Chlorid Concentration			Blood With- drawn, O c
	Amount	Duration	Avenue	Time of Observation			Hema- to-crit, %	Red Blood Cells, %	Whole Blood, Gm per Liter	Plasma, Gm per Liter	Cells, Gm per Liter	
4 24 kg	3 cc	½ min	Intra- venous	Before 3 min after 20 hrs after	43.7 30.9 25.0		100 141		4.68 6.15 4.76	6.01 7.25 5.71	2.98 3.72 1.92	17 18 17
5 32 kg	7 cc	1 min	Intra- venous	Before 5 min after 13 min after 24 hrs after	32.6 29.0 25.0		100 112 130		4.76 5.52 5.39 5.52	5.79 6.68 6.49 6.59	2.62 2.69 2.12	7 7 7 7
6 22 kg	5 cc	1 min	Intra- venous	Before 2 min after 12 min after 1½ hrs after 8 hrs after 24 hrs after	46.0 34.6 36.4 32.8 24.0 18.0		100 133 126 140		5.70 6.87 6.92 6.56			5 5 5 5
7 28 kg	18 cc	1 min	By stomach tube	Before 10 min after 1 hr after 24 hrs after	36.6 30.9 30.6 29.0		100 118 119 126		5.85 6.19 7.01 7.25	7.36 7.49 8.35 8.42	3.25 3.30 3.98 5.10	6 7 6 6
8 25 kg	18 cc	1 min	By stomach tube	Before 5 min after 30 min after 24 hrs after	19.6 17.8 18.4 14.5	2,720,000 2,592,000 2,096,000 1,992,000	100 110 106 135	100 105 130 136	5.64 5.80 6.30 6.99	6.51 6.72 7.20 8.00	2.09 1.57 2.12 1.03	7 7 6 7

not obtained so that precise relationships between blood volume and blood salt are not intended. In experiments 7 and 8, the hypertonic salt solution was administered by stomach tube, the blood volume becoming progressively higher during the twenty-four hours following the ingestion of the salt, and the chlorid concentration of the blood steadily rising in parallel fashion. It becomes apparent from these data that in the case of rabbits unable to excrete salt the retention of chlorids in the blood is associated with the retention of an increased plasma volume.

There are other factors that have a more or less obvious bearing on the elevation in blood volume due to hypertonic salt solution. The slower the speed of administration, the less will be the amount of increase in blood volume, since the increased fluid is constantly leaving the blood stream. Where a uniform amount of solution is administered, the weight of the subject will be an evident factor. In Case 1, it was seen that 6.78 gm of salt were found increased in the blood two minutes after the first injection of 15 gm, and 10.56 gm one-half minute after the second injection of 15 gm. Granting that a certain amount of chlorids were excreted through the kidney and intestine, it is evident that the larger part was taken up by the tissues. Before the first injection the total chlorids, as well as the chlorid concentration were low, whereas before the second injection the total chlorids and the chlorid concentration were considerably higher. This suggests that the paucity of body chlorids in the first instance was responsible for the tissues taking up more chlorid than in the second instance, in which the chlorid concentration and total chlorids were already relatively high. The suggestion is purely a tentative one, and it must be admitted that the differing time intervals following the injection may be partly the cause of the discrepancy.

From our results in the series of patients studied, no typical curve of blood volume following the administration of hypertonic salt solution was found. It is obvious that there are sufficient reasons for this. The persons studied were not normal but severely ill. The treatment of each patient varied, and the diet and fluid intake likewise varied according to the therapeutic indications. Although a uniform amount of solution was generally given, this meant a varying dosage in terms of salt per kilogram of body weight. The speed of injection, as well as the time of making observations, was not kept constant. No typical response of the blood volume was thus found but certain general characteristics can be described as well as the probable mechanism.

After the intravenous injection a rapid rise in blood volume was followed by a gradual fall. The greatest increase appeared to be present immediately after, i. e., 30 seconds after the end of the injection. In all of the determinations, except one, a substantial return toward the original blood volume occurred in from one to three and

one-half hours after the injection (Tables 1, 2 and 3) In the one case referred to the elevated blood volume persisted for four days, an observation which was confirmed by a vital red determination Estimations of blood volume from hemoglobin determinations twenty-four hours after the injection cannot be considered reliable, as pointed out earlier in this paper It is believed, however, that relative variations in blood volume can fairly be told from hemoglobin determinations taken within from one to four hours of each other

TABLE 5—RELATIVE BLOOD VOLUME FOLLOWING INTRAVENOUS ADMINISTRATION OF HYPERTONIC SALT SOLUTION

Experiment Number and Weight of Animal	Injection of 15% NaCl			Hematocrit Red Cells, %	Blood Volume Calculated from Hematocrit, %	Blood Withdrawn, C c	Remarks
	Amount	Duration of Injection	Time of Observation				
1 3 kg Rabbit	8 c c	1 min	Before	24.0	100	1	Marked tachypnea
			7 min after	13.5	178	1	
			22 min after	16.5	155	1	
			26 min after	17.3	139	1	No ill effects
			1½ hrs after	18.5	130	1	
2 3 kg Rabbit	3 c c	1 min	Before	30.0	100	1	No ill effects
			½ min after	27.0	111	1	
			5 min after	27.0	111	1	
			30 min after	27.5	109	1	
			45 min after	27.0	111	1	
			2 hrs after	27.0	111	1	
			3 hrs after	21.5	139	1	
			24 hrs after	21.2		1	
3 3.5 kg Oat	7 c c	1 min	Before	36.6	100	15	Ether anesthesia
			3 min after	23.9	153	15	
			1 hr after	30.0	122	15	

It is interesting to note that the example of a persistently elevated blood volume occurred in a patient who had an abnormally low plasma volume associated with a low blood chlorid concentration and a low total chlorid content After the first injection, the plasma volume and the chlorid figures were approximately normal, and maintained their normality until the second injection After the second injection, a rapid rise in blood volume occurred, followed by a substantial return to the previous figure in three and one-half hours, as shown by the hemoglobin determinations Similarly, after the third injection, the relative blood volume (as calculated from the hemoglobin, red corpuscle, and hematocrit dilution) showed a sharp elevation, followed by a gradual fall, approaching normal in three hours (Table 1) The reason for this variation in response may, perhaps, be found in the tendency of the organism to revert to or maintain the normal In the presence of a low blood volume and a low total chlorid content the increase in volume and chlorid content of the blood persisted In the presence of a normal blood volume and blood chlorid the elevation above the normal on two occasions was quite temporary, returning largely to the normal

figures within three and one-half hours. It is freely admitted that this reasoning is hypothetical and may not at all account for the facts.

It was shown in Case 1 that the increase in blood volume was approximately equal to the number of cubic centimeters of water theoretically required to render the increased chlorids in the blood isotonic. On this basis, the maximum increase due to administration of 15 gm salt would be 1,666 c c. As a matter of fact, however, this amount is never actually reached since a certain portion of the chlorids enters the tissues or is excreted the moment it arrives in the blood stream. The maximum increase, expressed in terms of relative blood volume, varied in individual cases from 115 to 130 per cent of the original blood volume. This would represent a range of increase of from 500 to 1,200 c c of tissue fluid. In the two instances in which the absolute blood volume was measured by the dye, the maximum increase was 761 c c after the first injection and 894 c c after the second injection.

In Case 4 (Table 2), 100 c c of 1,500 per cent Ringer's solution (fifteen times stronger than standard Ringer's solution) was injected. This patient was unrelieved of his headache, and there was no fall in spinal pressure, as shown by manometer readings. It is interesting to note that the increase in blood volume and in blood chlorids was of very slight degree. The reason for this can, in part, at least, be accounted for by the lessened amount of chlorids present in Ringer's solution, but the changes still seem of lesser degree than one would expect. The serum directly following the injection was deeply hemolyzed, an effect presumably due to the excess potassium in the solution. It is of some interest to note that in this case a hypertonic salt solution was given without any fall in cerebrospinal pressure, and with minimal evidence of blood dilution. In the other cases so tested, the fall in cerebrospinal pressure was accompanied by considerable blood dilution. The findings strongly suggest that the drop in cerebral pressure when it does occur is due to a volume change dependent on egress of fluid from the brain to the blood stream.

In the two persons to whom the salt was administered by mouth either a smaller amount or a smaller concentration was given. The result was that a much smaller increase in blood volume occurred and that the maximum increase took place more than one-half hour after the injection rather than immediately afterward. The rabbits received a much larger dose by mouth than they did intravenously, but the resultant increase in blood volume was about the same in the two groups. The two rabbits, which received the salt by mouth showed a progressively increasing blood volume associated with a progressively increasing blood concentration, as was discussed above. It may be mentioned in this connection that Foley and Putnam¹⁹ found that the

oral administration of hypertonic salt caused a fall in cerebrospinal pressure similar to the intravenous administration provided that larger amounts of salt were given

Red Corpuscles and Hemoglobin—There were no significant changes in the red blood cells, except their decrease in number due to dilution. No hemolysis occurred as a result of hypertonic sodium chlorid injection. In the case in which hypertonic Ringer solution was given, the hemolysis was probably due to the abnormal amount of potassium present. Examination of the serum spectroscopically for traces of hemoglobin or for increased amounts of bilirubin was done in two cases with negative results³⁹

In Case 2 (Table 4) the red cells showed a slight increased resistance to hypotonic saline three minutes after injection with a return to the normal fragility twenty-four hours later. Before the injection the chlorid content of the red corpuscles was 0.64 gm per liter, three minutes after 0.75 gm per liter, twenty-four hours after 1.50 gm per liter. The finding of temporary lessened fragility is probably explainable on the supposition that the increased chlorid content of the cell had not been reduced to isotonicity within three minutes. In this case it appears that the red corpuscles had swollen at the end of twenty-four hours, inasmuch as the hemoglobin and red blood cell count still showed dilution and the hematocrit had largely returned to the original value. The striking increase in the chlorid content of the red cell from 0.64 to 1.50 makes this seem plausible. In Case 3 (Table 2) the fragility test was made with control cells but with equal quantities of the plasma before and after the injection of hypertonic salt solution. No change in fragility resulted from admixture with plasma taken after the salt injection.

Oxygen and Carbon Dioxid Content of Venous Blood—The venous oxygen content was markedly lowered, reflecting and largely due to the diminution in oxygen capacity. There was in one instance (Case 2, Table 2) a lowering of the venous saturation that may have represented a slight slowing up of blood flow due to sudden increase in blood volume. In the other three cases, the lowering of the venous saturation was too slight to be significant. The carbon dioxid content of venous blood showed no constant or decided changes in the three cases in which this was carried out (Table 2).

Clinical Results—No harmful effects following the administration of hypertonic salt solution were observed. The precaution was taken to exclude any case that gave evidence of renal disease. The six patients with brain tumor who had increased cerebrospinal pressure were all symptomatically improved. The symptoms that were especially relieved

³⁹ These examinations were performed by Dr. Chester M. Jones.

were headache and stupor (remarks in Tables 1, 2 and 3) In one instance a patient was inarticulate before the injection and afterward could make herself understood by a slurring speech The relief of symptoms generally lasted one day One patient, who for six weeks had suffered continuously from severe headache and stupor, became wide awake and completely free from headache twenty minutes after the injection, and remained so for three days, when her symptoms began gradually to return Among the immediate effects was the sensation of feeling very hot All the patients who were able to talk complained of it This disappeared within twenty or thirty minutes of the injection There was a temporary rise in pulse rate of between five and fifteen beats and in systolic blood pressure of between 10 and 40 mm, maximal immediately after the injection and returning to normal usually within thirty minutes of the injection In no instance was there a rise in temperature of more than 1 degree (F) In the patient, who had a fracture of the skull and to whom 1,500 per cent Ringer's solution was given, no beneficial effects were observed In the patient with polycythemia to whom the salt was administered by mouth, no definite change in condition was manifest

SUMMARY AND CONCLUSIONS

1 Hypertonic salt solution was administered intravenously to six patients with brain tumor and to one patient with a fractured skull, by mouth to one patient with polycythemia and to one normal person, intravenously and by mouth to eight rabbits Observations were made on the blood volume, the blood chlorid concentration, the total chlorid content of the blood, the effects on red corpuscles and hemoglobin, the venous oxygen and carbon dioxid content, and the clinical condition of the patients

2 The immediate effect of the intravenous injection of 100 c c of 15 per cent sodium chlorid solution was a marked increase in plasma volume Reckoned in terms of relative blood volume, the increase was between 15 and 30 per cent of the original blood volume, and the calculated increase on this basis between 500 and 1,200 c c of tissue fluid In two instances in which the absolute blood volume was determined by the vital red dye method the maximum increase in one case was 761 c c and in the other 894 c c The increase in blood volume reflected and was almost wholly due to the increase in plasma volume

After the injection there was a more gradual fall in blood volume, in most cases largely, although not entirely, returning to the original volume within three and one-half hours In one case that had an abnormally low blood volume the increase persisted for four days

3 An increase in blood volume followed the oral administration of hypertonic sodium chlorid, but was relatively of lesser degree and slower onset

4 The mechanism of elevation and maintenance of the blood volume after hypertonic salt administration appeared to be dependent on the behavior of chlorids in the blood. Following the injection of 15 gm sodium chlorid solution in two determinations in Case 1, there was found an increase of approximately 6 gm in the first and 10 gm in the second

In the first instance the amount of increase in plasma volume was equal to the amount of water theoretically required to render the increased chlorids isotonic. In the second instance the plasma volume increase was slightly less than the theoretic requirement of the added chlorid, indicating that in a portion of the blood stream at least the blood was slightly hypertonic. Essentially, however, the increase in blood volume corresponded to the isotonic equivalent of the introduced salt. In the other human cases and in the animal experiments the rise and fall in blood volume generally ran approximately parallel to the blood chlorid concentration

In rabbits showing an inability to excrete chlorid, the increased blood volume persisted elevated with a parallel maintenance of the increased blood chlorid concentration

5 The red corpuscles showed no impairment due to the introduction of hypertonic sodium chlorid solution. In one case there was a temporary lessening of fragility. The oxygen carrying power of the hemoglobin was intact. There was no free hemoglobin spectroscopically, or any increase in bile pigment. In one patient, to whom a markedly hypertonic Ringer's solution was given, evidence of hemolysis appeared in the serum, due presumably to the abnormal amount of potassium present

6 No significant changes in oxygen saturation or carbon dioxide content of the venous blood were found

7 In the six patients with brain tumor, who had an increased cerebrospinal pressure, symptomatic improvement occurred in all. This was mainly manifested in the relief of headache and stupor. No harmful effects were observed. It appears likely that the fall in cerebrospinal pressure that follows the intravenous or oral administration of hypertonic salt solution is a volume change dependent on the egress of fluid from the brain to the blood stream

We wish to express our thanks to Dr Stanley Cobb and Dr James B. Ayer for finding us neurologic cases at the Massachusetts General Hospital, and to Dr James H. Means for his interest and aid during the course of the work

BOOK REVIEW

ROENTGEN-RAY DOSAGE IN TREATMENT AND RADIOGRAPHY By W D WITHERBEE and JOHN REMER

This book sets forth the authors' views on filtered and unfiltered dosage by roentgen rays, and gives a bird's-eye view of the field of usefulness for roentgen-ray therapy. Such information has been in great demand since the use of the rays has been so widespread. The quantities given for filtered roentgen-ray dosage assume the theory that at twice the skin-target distance the therapeutic effect is one-half as great. This is contrary to the statements of other writers and is contrary to the accepted laws for radiant energy which state that the quantity of rays varies inversely as the square of the distance. Readers who are accepting the quantities set down for filtered dosage should be aware of this departure from the usual computations and measurements.

THE PATHOLOGY OF BRONCHIAL ASTHMA*

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INTRODUCTION

In a clinical study of a certain type of food asthma, published nearly ten years ago,¹ one of us expressed the conception that bronchial asthma is a manifestation of allergy in the human, in the following concluding sentences "In most cases of bronchial asthma the causative factor lies in the allergic reactivity of the individual" and, "The multiplicity of asthmato-genous substances is explained by the multiplicity of proteins which may act as anaphylactogens."

The later clinical and immunologic studies of Walker, Cooke, Rackeman, and Mackenzie, undertaken from the same point of view have greatly elaborated the evidence for this conception and have brought forward more detailed proofs for its correctness and general validity for the majority of all cases of asthma. Since allergy in the end means changed tissue reaction, it is obvious that the investigation of any allergic condition in the human must necessarily take up the question whether demonstrable morphologic changes are associated with the physicochemical changes which are the first reactions of the organism toward the protein acting as an allergen.

The histologic examination of the animal body postmortem has furnished, in one particular form of allergy, anaphylaxis, very important information which is of the greatest value in the diagnosis and characterization of the anaphylactic death and for our understanding of the pathologic physiology of this immunologic phenomenon. It suggests at the same time that different organ-systems and structures are primarily involved in different species of animals, and opens the still unanswered question whether all tissues of the same species are allergic to the same extent.

Up to the time of the allergic conception of bronchial asthma, the students of this disease, neglecting too much the true underlying

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1 Koessler, K K. Bronchial Asthma Due to Hypersusceptibility to Hen's Eggs. Illinois M J 23 66, 1913

condition, had focused their chief attention on the respiratory crisis, the paroxysmal attacks of dyspnea. This symptom fascinated the physician on account of its explosive and dramatic character and, because of the intense discomfort of the patient, demanded immediate relief, often taxing the resources of medical aid to the utmost. While the respiratory crisis of asthma comprises in itself no more of the pathologic physiology and true nature of the disease than do the convulsive attacks in eclampsia or epilepsy, it has developed in this way that most discussions of this condition have dwelt chiefly on the origin and mechanism of the dyspnea.

The theories that have been formulated to explain the attacks of paroxysmal dyspnea are agreed today that the difficulty of respiration is due to a stenosis of the bronchi, but whether this narrowing is due chiefly or exclusively to a spasm of the bronchial smooth muscle system, to swelling and exudation of the bronchial mucosa, to a true obturation stenosis by the secretion from the bronchial glands, or to a combination of two or more of these conditions seems still to be an unsettled question. The recognition that certain forms of bronchial asthma are manifestations of allergy in man, a conception which has introduced a new era in the study and treatment of this disease, has strengthened the contention that bronchiolar spasm is the important factor in the production of the bronchostenosis. It must be admitted, however, that this view, aside from the indirect proof obtained from the pharmacologic action of atropin and epinephrin, has mainly been deduced from the mental comparison and identification of the emphysema and bronchospasm observed in the classical experiment of anaphylaxis in the guinea-pig and not from a detailed study of the lung structures of the human asthmatic after death.²

The diffuse and loose application of the term "anaphylaxis" to every kind of diurnal or nocturnal dyspnea will not advance our knowledge of bronchial asthma. Anaphylaxis is a well defined immunologic phenomenon, and the application of this term should be restricted to those forms of asthma which fulfil at least some of the following conditions:

- 1 Positive skin sensitization tests for one or more specific proteins. It is possible, however, to be sensitized in the allergic sense and to show no skin sensitization.³

- 2 Blood, sputum and tissue eosinophilia, showing an altered reaction of the human organism to a foreign soluble protein.

² Meltzer, S. J. Bronchial Asthma as a Phenomenon of Anaphylaxis, *J. A. M. A.* 55 1021 (May 9) 1910.

³ Fleischer, E. C., Meyer, K. F., and Shaw, E. B. A Resume of Some Experimental Studies on Cutaneous Hypersensitiveness, *Am. J. Dis. Child.* 18 577 (Dec.) 1919.

3 Relief from the bronchial spasm by the use of atropin or epinephrin

4 Desensitization of the patient by repeated injections of the exciting protein, e g, horse dander, pollen or by ingestion of gradually increasing quantities of the exciting protein, e g, egg-white

5 Freedom from symptoms on removal of the exciting protein

6 Passive sensitization of a laboratory animal with the blood of the asthmatic

7 Postmortem examination in fatal cases to determine if there are any changes which account for the sudden death and which simulate the acute emphysema found post mortem in the guinea-pig and to exclude the dyspnea due to capillary thrombosis or embolism (anaphylactoid reaction of Karsner and Hanzlik), for it is chiefly the pathologic-anatomic examination of the animals postmortem that has characterized the anaphylactic symptom complex peculiar for each species

On the other hand, we believe it to be a grave mistake to consider all cases of bronchial asthma as a manifestation of allergy. The fallacy becomes especially apparent in a study of the bacterial type of asthma, the so-called asthmatic bronchitis.⁴ Bacterial infection may lead in a variety of ways to bronchial stenosis. The infection of the mucosa and the glandular structures may produce an abundant exudate leading to partial or total obstruction of certain bronchi, or the infection may lead to profound injuries of the protecting layer of the mucosa, causing minor losses of substance, thus facilitating absorption of toxic materials which stimulate muscular spasms similar in mechanism to the bronchiolar spasm produced through inhalation of excoriating gases. It is also not improbable that various poisons of the type of peptones or amines are formed by the action of bacteria on tissue proteins. These poisons, when carried by the blood or lymph stream from the intestinal tract, or from distant foci of infection to the peripheral nerve endings in the bronchial musculature, may stimulate it to spastic contraction. Only in very rare instances might bacterial proteins, as such, sensitize a person and act as anaphylactogens. Then the bacterial type of asthma, too, might become allelgic in character. Even in the instances of allergic asthma a chronic bronchial infection is often superimposed as a second pathogenetic factor, which only too often obscures, especially in older persons, the primary allelgic susceptibility of the patient.

⁴ Koessler, K. K., and Moody, A. M. Etiology of Chronic Bronchitis, with Special Consideration of Those Forms Associated with Bronchial Asthma, *J. A. M. A.* **64** 1104 (March 27) 1915

These considerations suggest that detailed histological examinations of patients who have died from asthma should furnish information of value for settling certain phases of the problem briefly discussed in the preceding paragraphs

HISTORICAL REVIEW

Since our work is mainly concerned with the microscopic analysis of the finer lung structure in bronchial asthma, we shall review here only those cases in literature in which a microscopic examination has been made. While the medical literature of the seventeenth, eighteenth and nineteenth centuries contains some excellent post-mortem reports on the macroscopic examination of persons who have died of asthma, the survey of these reports does not, at this time, warrant their inclusion here for the sake of completeness. The number of recorded microscopic studies of the lung structure of persons who, during life, have suffered from true bronchial asthma, is exceedingly small if one considers the frequency of the disorder. So far as we know, only fifteen cases are reported in which a more or less detailed microscopic study of the lungs has been made and of this number only about one-half seem, on close analysis of the data, to be cases of true bronchial asthma.

SUMMARY OF CASES IN LITERATURE

CASE 1 1886 E v Leyden —*History*—Female, aged 40, had had asthma

NECROPSY REPORT Macroscopic Examination—Both lungs show marked vesicular emphysema and their borders are greatly distended. The bronchi are not dilated and not changed except for a reddening of the mucosa. The small bronchi contain greenish or whitish mucous masses in which there are no fibrin or crystals.

Microscopic Examination—Some of the alveoli are distended, while others are not, and most are filled by a granular material containing many large cells. The walls of the smaller bronchi are not essentially changed and the lumen of many is practically occluded by a layer of amorphous material which is adherent to the epithelium. One illustrated section is described.

Comment—From the history, this case appears to be a typical case of bronchial asthma which was complicated during the last months of life by failing heart and kidneys. The occlusion of many bronchi by mucus is the most significant pathologic change described.

5 v Leyden, E Ueber Bronchial Asthma, Deutsch Militärarztl Ztschr 15 51, 1886, Ueber Bronchial Asthma, Berlin, 1886, Mittler and Son since early childhood and was treated by v Leyden seven years previously. Her attacks appeared and disappeared suddenly, the frequency, severity and number varying considerably. In attempting to relieve her suffering she became a high grade morphin addict. Later severe hydrops and albuminuria developed. The lungs were emphysematous and sibilant râles were diffuse. During attacks, a tough grayish sputum containing fibrinous threads, small firm masses, crystals and epithelial cells were raised. Death followed an attack of severe dyspnea with cyanosis.

CASE 2 1889 J B Berkart⁶ *History*—Mrs C, aged 37, family history of tuberculosis Childhood diseases whooping cough, measles and scarlet fever Since childhood she had been subject to frequent colds, especially in early summer The first attack of bronchial asthma followed a severe prolonged bronchitis at the age of 23 Following this, she had frequent attacks of bronchitis with asthma which, with a swelling of the legs, caused her to enter the hospital a few months before death On entrance, the heart's action was disturbed and the urine contained albumin She left the hospital after a stay of three or four months, being considerably improved, except for a generalized edema and frequent severe attacks of paroxysmal dyspnea Nine days before death she was seen again because of dyspnea, cough, insomnia, diarrhea and weakness The face was cyanotic and edematous The chest showed bilateral high pitched resonance with diffuse sonorous and sibilant ronchi Pulse 100, small, soft and regular Heart extended beyond the right sternal border and its sounds were loud and clear Abdomen distended Urine negative Twenty-four hour specimen of sputum about 4 ounces, contained Curshmann's spirals, Charcot-Leyden's crystals and eosinophils Death followed an acute exacerbation of all her symptoms

NECROPSY REPORT *Macroscopic Examination*—Heart, considerable dilatation and hypertrophy, with valves intact Lungs not collapsed Extensive adhesions of the right apex The right main bronchus and one branch of the left main bronchus are almost occluded by dark brown cylindrical branching masses The smaller bronchi are dilated and some are partially obstructed by exudate The rest of the lungs are emphysematous The abdomen contains a moderate amount of fluid The liver, spleen and kidneys are large, pale and dry

Microscopic Examination—The cylindrical masses are composed chiefly of deformed degenerating cylindrical epithelium with no Charcot-Leyden's crystals The mucous membrane of the right main bronchus shows firm, fibrous avascular excrescences covered by a single layer of oblong epithelium, almost all the remainder of the mucosa being denuded One deep ulceration in a main bronchus extends almost to the cartilage There are a few colonies of staphylococci between the folds of the internal fibrous layer The mucous glands are remarkably few in number, very small and looking as if atrophied The bronchi of medium size are irregularly dilated, most of them partially or completely occluded by masses of detritus containing fragments of Charcot-Leyden's crystals The walls are thickened and there is considerable hyperplasia of the mucous membrane The finest bronchi are dilated and denuded of epithelium and some contain fibrinous threads and colonies of streptococci The alveoli are emphysematous and have no epithelium, while some are almost filled with a fibrinous exudate

Comment—The clinical history of the case points to a bronchial asthma developing from a chronic bronchitis and complicated in the last few months by a failing heart The most significant pathology is the ulceration in one of the chief bronchi, the atrophy of the mucous glands and the hyperplasia of the mucosa of the middle sized bronchi

CASE 3 1892 A Schmidt⁷ *History*—J S, waitress, aged 49, previous illness articular rheumatism at 44 Six months before death, dyspnea, emaciation and weakness caused the patient to stop work Two months before death a troublesome cough, which was relieved by raising a small amount of

6 Berkart, J B Bronchial Asthma, London, 1889

7 Schmidt, A Beitrage zur Kenntniss des Sputums insbesondere des Asthmatischen und zur Pathologie des Asthma bronchiale, Ztschr f klin Med 20 476, 1892

tenacious mucus, developed and she was unsuccessfully treated for bronchitis. About three weeks before death the first typical attack of asthma came on and was relieved an hour later by raising some tenacious mucus. Following this, attacks came on frequently and she entered the hospital. Examination showed an emaciated female with a cystic growth the size of a goose egg in the left side of the neck. The lung borders were lowered and many dry rales were heard on expiration. Severe attacks came two to three times daily and three days after entering the hospital she died in collapse following a severe attack of dyspnea.

NECROPSY REPORT *Macroscopic Examination*—Tumor nodules press against and partially encircle the structures in the left side of the neck, occlude the thoracic duct and extend into the mediastinum and into the upper lobes of both lungs. A small tumor mass presses against the left pulmonary vein and partially occludes it. The heart is large and shows a marked fatty degeneration. The right ventricle is dilated. The aorta is markedly sclerotic. The apices of both lungs are adherent to the thoracic wall. The section of both lungs shows numerous tumor nodules in the upper lobes, some of which at the hilum press on the bronchi and cause narrowing of their lumina and degeneration of their walls. Peripheral to the narrowed places, the bronchi are dilated. The bronchi of both upper lobes contain yellowish tenacious mucous masses which can be pressed out or pulled out as long spirals, several centimeters in length. Both lower lobes contain much blood and exude a purulent fluid. Neither contain tumor nodules except at the hilum. The remaining organs show no important change.

Microscopic Examination—The epithelium of the dilated bronchioles is almost intact, the lumen almost or completely occluded by mucous material which stains more deeply in the central portions and contains numerous cells, among which are alveolar epithelium, a few polymorphonuclear neutrophil leukocytes and some homogeneous round, oval or elongated structures without nuclei. The mucus in the bronchioli respiratorii shows the spiral arrangement but the alveoli contain no spirals. The mucous glands of the bronchi are in a state of active secretion, but the gland ducts contain no spirals. The walls of the bronchi and bronchioles contain dense connective tissue fibers and are infiltrated by round cells. Surrounding a few of the bronchi, which contain polymorphonuclear leukocytes, the alveoli contain numerous leukocytes of the same type. The blood vessels of the upper lobes show a marked periarteritis obliterans. The masses of tumor tissue have the arrangement of a medullary carcinoma.

The author discusses the occurrence of Curshmann's spirals, Charcot-Leyden's crystals, fibrin and eosinophil cells in the sputum and shows that, as these structures are found in so many other disorders, the sputum findings are of no great diagnostic importance in bronchial asthma. He considers the attacks of dyspnea as the all important symptom, but believes that there is no sharp distinction between the dyspneas of asthma and of severe bronchitis. But, he says, the work of Biermer and others has shown that there is a distinct nervous form of asthma in which the inflammatory factor is insignificant and he considers this form as proof that the nervous system plays an important rôle in the spasmodic element in the common exudative form of asthma as well, which fact sets asthma apart as a morbid entity distinct from bronchitis.

Comment—Two important points must be considered in this case. First, the initial attack of asthma occurred within the last three weeks of life, and second, the presence of tumor masses pressing against the structures of the neck, mediastinum and lung. We question, therefore, whether this is to be considered as a typical case of bronchial asthma or whether it is rather to be classed as a symptomatic asthma due to a medullary carcinoma involving the respiratory tract.

CASE 4 1898 A. Fraenkel⁸ *History*—Male, aged 63, carpenter. Previous illnesses: rheumatism and gout for years, bronchial catarrh since 60 and followed two years later by asthmatic attacks. About six weeks before death the patient entered the hospital suffering from gout, emphysema, chronic bronchitis and frequent asthmatic attacks. During attacks the lung borders were lowered and numerous râles were heard all over the chest. The sputum contained a few Charcot-Leyden's crystals but no Curschmann's spirals. The patient improved steadily for a time but died suddenly during a severe attack after a five-day period of freedom from attacks.

NECROPSY REPORT *Macroscopic Examination*—Both sides of the heart are dilated. The lungs are distended and almost cover the pericardium. The right lung is slightly adherent to the chest wall. The bronchi on both sides are dilated, their mucosa is reddened and they contain a mucous material which can be pulled out threadlike. The bronchial glands are greatly enlarged and pigmented.

Microscopic Examination—In the stained sections of the bronchial clots there are no typical spirals, but twisted threads, resembling fibrin, are present. The epithelium of the middle sized bronchi is detached from the basement membrane and forms twisted rows of cells which completely occlude some of the bronchi. Some of these cells are greatly elongated. The denuded wall appears thickened and contains many dilated capillaries and round cells. Some of the alveoli are emphysematous and some are compressed, while some contain a few blood cells. In some places the interstitial connective tissue is increased.

Comment—To us, the most interesting points in this case are the history of a chronic bronchitis, the advanced age of the patient when the first attack occurred (62), attacks for only one year before death and the necropsy findings of an adhesive pleuritis and a thickening of the bronchial walls. It may be questioned whether this is a typical case of bronchial asthma or is a senile dyspnea due to a combination of a chronic bronchitis, emphysema and a failing myocardium.

CASE 5 1900 A. Fraenkel⁹ *History*—Male, aged 48. For about one and a half years preceding death the patient remained in the hospital suffering from almost daily severe asthmatic attacks, during which he raised a tenacious mucus containing Curschmann's spirals and Charcot-Leyden's crystals. The last severe attack resulted in death thirty-six hours later from collapse.

NECROPSY REPORT *Macroscopic Examination*—The middle-sized and smaller bronchi of both lungs are almost or completely occluded by screw-shaped clots.

8 Fraenkel, A. Zur pathologischen Anatomie des Bronchialasthmas, *Ztschr. f. klin. Med.* **35** 559, 1898.

9 Fraenkel, A. Zur Pathologie des Bronchialasthma, *Deutsch. med. Wchnschr.* **17** 269, 1900.

which can be pulled out with difficulty. In the larger tubes these clots are looser and several centimeters in length.

Microscopic Examination—Stained (Bondi-Heidenhain) specimens of these clots show them to be true mucus, the threadlike central portions staining more intensely than the outer portions, which contain numerous eosinophil cells. In the smaller bronchi from 0.15 to 0.03 mm in diameter, isolated epithelial cells are elongated to about 204 microns in length, resting on a layer of small round cells, the ciliated borders of some are ruptured and the mucous content of the cell protrudes as a drop in the lumen often fusing with a neighboring drop. In places these cells appear drawn out to form awl-like figures, in others they are heaped up to form layers two or three cells deep. The alveoli are almost free of secretion, containing only a few epithelial and eosinophil cells, and their walls contain dilated capillaries and collections of mononuclear and polynuclear cells. The walls of the small bronchi contain dilated capillaries and are infiltrated from the epithelium to the outer layer by cells, most of which are mononuclear and polymorphonuclear eosinophil cells. These cells are most numerous in bronchi containing glands and cartilages. Charcot-Leyden's crystals are found in places where the eosinophil cells are grouped.

Comment—This seems to be a true case of bronchial asthma of several years' duration. The most important finding is the microscopic evidence of an extensive chronic infection of the bronchi. It is of especial interest that most of the cells infiltrating the bronchial walls are eosinophilic.

CASE 6 1905 Jezierski¹⁰ *History*—Male, gardner, aged 63. Father died of asthma. Patient first had cough with dyspnea about five years before death and in the last two years of life the symptoms were so severe on two occasions that hospital care was needed. The symptoms consisted chiefly in attacks of severe expiratory dyspnea, sensation of fear, palpitation with tachycardia, pain in the epigastrium and cyanosis.

Physical examination showed a barrel-shaped chest, wide intercostal spaces, lowered lung borders, difficult expiration, and numerous dry and moist râles. After a six months' stay in the hospital the patient contracted a right lobar pneumonia and died two days later.

NECROPSY REPORT Macroscopic Examination—The upper and middle lobes of the right lung are large and of liver-like consistency. The left lung is small and light and the mucosa of its dilated bronchi is reddened.

Microscopic Examination—The bronchial lumina of the left lung, which is free from pneumonia, contain mucous masses in which are embedded cell remnants, well preserved ciliated epithelial cells often in rows, leukocytes, lymphocytes, erythrocytes and eosinophils. No fibrin is found. The well preserved epithelium is infiltrated by numerous round cells which invade all layers of the bronchial wall and in places are collected into groups resembling lymph glands. Beneath the epithelial layer the elastic tissue is markedly increased. There are also an unusual number of thin-walled closely-crowded capillaries around the tunica propria. The diaphragm shows some rarification and fatty infiltration. The neck muscles, the vagi and the cervical nerves show no changes, but the phrenic nerve contains groups of degenerating fibers. The right lung is a typical pneumonic lung.

Comment—The clinical history of attacks of dyspnea for about five years before death in an old man and the microscopic evidence

¹⁰ Jezierski. Zur Pathologie des Asthma bronchiale, Deutsch Arch f klin Med 85 342, 1905.

point to infection in the respiratory tract as a probable etiologic or complicating factor in the production of the asthmatic attacks, but the hereditary factor, the occupation and the presence of eosinophils point to an allergic pathogenesis. The most significant pathologic findings are the mucous masses in the bronchi, the cellular infiltration in the bronchial wall, the presence of eosinophil cells and the increase in elastic tissue.

CASE 7 1905 Jezierski¹⁰ *History*—Female, aged 46, silk weaver. Asthmatic attacks began twelve years previously. Patient entered the hospital a short time before death suffering from dyspnea, cyanosis and tachycardia. The lung borders were lowered and there were many buzzing and whistling râles on expiration. Death followed collapse during a severe attack.

NECROPSY REPORT *Macroscopic Examination*—Each pleural cavity contains about 200 c.c. of a bloody serous fluid. The left lung is markedly emphysematous and contains much blood. The bronchial lymph glands are anthracotic. Small wormlike mucous masses can be pressed from the small bronchi. The right lung contains fewer of these masses than the left.

Microscopic Examination—The mucous masses contain many elongated ciliated epithelial cells, some of which are drawn out as long filaments, cuboidal cells from deeper layers of the epithelium, round cells, numerous eosinophil cells, some erythrocytes and cellular debris. These constituents vary considerably in numbers and distinctness in different sections. The epithelium of the bronchi is intact, except in a few places where it is penetrated by round cells which infiltrate the bronchial wall either diffusely or are collected in groups about vessels. This infiltration is so marked in the smaller bronchi that all structures are obscured. The elastic tissue is not increased and there are no new-formed blood vessels. The lung parenchyma is intact.

Comment—The most significant pathologic findings are the occlusion of many bronchi by mucous masses and the extensive cellular infiltration of the bronchial walls. Many of these cells are eosinophils. While the microscopic evidence in this case points to infection as a probable etiologic factor in the production of the asthmatic attacks in this case, the clinical and necropsy evidence implicating the heart cannot be overlooked.

CASE 8 1908 A. G. Ellis¹¹ *History*—Coachman, aged 27, had been under treatment for tachycardia and bronchial asthma during the preceding year, and the day before death was admitted to the hospital during an asthmatic attack, with severe expiratory dyspnea, cough and cyanosis of face and extremities. The attack persisted and the patient collapsed and died the following day.

NECROPSY REPORT *Anatomic Diagnosis* Hypertrophy of the left ventricle, dilatation of the right ventricle, pulmonary emphysema, purulent bronchitis, exudative bronchiolitis.

Macroscopic Examination—The lungs are distended and entirely cover the pericardium. The right lung is slightly adherent to the thoracic wall and both lungs on sections show shiny, often greenish-colored plugs in the smaller bronchi.

Microscopic Examination—Sections taken from various parts of both lungs reveal the following changes. The alveoli are distended only in patches and

¹¹ Ellis A. G. Pathological Anatomy of Bronchial Asthma, Am J M Sc 136 407, 1908.

those bordering the bronchi contain mucus, some leukocytes and a few eosinophil cells. The capillaries are uniformly engorged. The lumina of most of the smaller bronchi, from 0.13 to 0.16 mm in diameter, are partly or entirely filled with a slightly granular mucus which is often arranged in distinct spiral form, the peripheral portions being less dense and containing a greater number of cells. These cells are chiefly polymorphonuclear leukocytes, among which are degenerated epithelial cells. The epithelium is mostly intact and averages about 7 microns in height. The bronchi, from 0.2 to 0.45 mm in diameter, contain mucus, sometimes with spiral arrangement. Some of the epithelium is retained, other portions are separated en masse from the basement membrane and in one place an eroded blood vessel is exposed. In bronchi 0.8 mm in diameter the amount of mucous material and desquamated epithelial cells varies, and some of the cells are much elongated (35 microns). In all these bronchi the mucus is arranged in layers, as is shown by the distinct longitudinal rows of cells. A few polymorphonuclear eosinophil cells are present in the lumina of all the bronchi. The walls of the bronchi and of the adjoining alveoli are infiltrated with leukocytes, the inner layer of the wall near the epithelium containing chiefly polymorphonuclear leukocytes, the outer layer containing chiefly large mononuclear cells with vesicular nuclei. Among these cells, especially in the middle sized bronchi, there are varying numbers of polymorphonuclear eosinophil cells. The capillaries in the walls are dilated and in some places small hemorrhages are found. The tunica propria and the basement membrane appear hyalin in some places. There is no change in the muscle or elastic tissue, and the connective tissue is not appreciably increased. The larger blood vessels of the lung contain more than the usual amount of blood and one contains a small thrombus.

Comment—The most important findings in this case are pleural adhesions of one lung, occlusion of many of the smaller bronchi by mucous masses and the cellular infiltration of the bronchial walls. The extensive cellular infiltration of the bronchial wall shows that a chronic infection was present at death. Without considering the clinical data, these two facts point to infection as a possible etiological factor in this case of bronchial asthma, but the presence of many eosinophil cells suggests an allergic pathogenesis.

CASE 9 1909 Monckeberg¹² *History*—Male, aged 29, mason. Previous illnesses, pneumonia in twelfth and again in eighteenth year. Psoriasis in twenty-fourth year. After serving in the army without any sickness from his twentieth to his twenty-second year, he first noticed in his twenty-fifth summer an irritating cough and dyspnea following a rapid march. He tried to be exempted from participation in some military maneuvers later that year because of this trouble, but failed. At this time, while in his quarters at night, he had severe attacks every four to eight days, and was later released from service. Following this, severe attacks came more frequently, often from five to six times daily, and for the rest of his life, about four years, he gradually grew worse, except for transient periods of improvement. A short time before death he entered the hospital because of dyspnea and a generalized edema. At this time he had a constant dyspnea which increased in severity, came in attacks every two or three hours and was relieved by coughing up much tough mucus, containing numerous spirals, eosinophil cells and leukocytes. The lung borders were not movable, and numerous vesicular and ringing râles were heard on expiration. The heart was rapid and irregular and the blood contained an increased number of

¹² Monckeberg, J. G. Zur Pathologischen Anatomie des Bronchialasthmas, *Verhandl d deutsch pathol Gesellsch* 14 173, 1909.

eosinophile cells The urine was not decreased in amount Death followed a series of severe attacks

NECROPSY REPORT *Anatomic Diagnosis* Desquamative bronchial catarrh with hypersecretion of mucus, spiral formation, eosinophilia and asthmatic crystals, vesicular emphysema, bilateral complete adhesive pleuritis, isolated chronic and fresh tubercles in both lungs and in the hyperemic enlarged lymph glands

Macroscopic Examination—Well-developed and well-nourished male with generalized edema Abdominal cavity contains much clear yellow fluid Thorax barrel-shaped Both pleural cavities are completely obliterated by adhesions The right heart is markedly dilated and its walls thickened The myocardium is a pale yellowish-brown color No valvular changes The mediastinal and bronchial lymph glands are large, soft and red Both lungs are dilated The cut surface of the lungs shows all the larger and most of the smaller bronchi to be completely occluded by tenacious, yellowish-white branching masses The bronchial walls are thickened and show two distinct zones, a thin inner grayish-yellow zone and an outer reddish zone The chief bronchi contain only some tenacious mucus not adherent to the wall The remaining organs show the usual findings of a chronic passive hyperemia

Microscopic Examination—Most of the emphysematous end branches of the bronchi and the alveoli are empty, a few containing fluid and epithelial cells and having thickened walls, some of which are infiltrated by mononuclear and polymorphonuclear cells, chiefly eosinophils The elastic fiber tissue is not increased, but the muscular tissue in the alveolar and lobular septa is increased The pulmonary artery is thickened and sclerotic throughout and some branches contain organized thrombi There are a few scattered new epithelioid miliary tubercles in the thickened cell-infiltrated connective tissue about the larger bronchi The walls of the pulmonary veins are diffusely thickened All capillaries are engorged by blood, and in places there are extravasations of erythrocytes into the tissue The bronchioles up to the diameter of 0.2 mm are either empty and with intact epithelium, or they contain bands of desquamated epithelial cells with interwoven cilia, a few "Herzfehlerzellen" and some mucus There are no inflammatory changes in the thin muscular layer of these dilated bronchioles The lumen of bronchioles, from 0.2 to 0.4 mm in diameter, contains somewhat more well-preserved desquamated epithelium, round cells and detritus, and the walls contain a few mononuclear and polymorphonuclear eosinophil cells The bronchial branches from 0.4 to 0.5 mm diameter have a stronger muscular layer, which is frequently interrupted by diverticula or cryptlike protrusions of epithelium (Schleimhautausstülpungen) The epithelium is mostly intact, and at the crests of the folds is crowded together and appears elongated The lumen contains cellular detritus, mucus, epithelial cells and round cells, often arranged in whorllike thickenings The walls are infiltrated by many round cells The walls of bronchi, from 0.5 to 1 mm in diameter, contain small cartilages and mucous glands, the muscular layer is markedly developed and the cryptlike diverticula are more numerous and some are branched The mucous glands which are in active secretion open into some of these diverticula The broadened and hyalinized basement membrane continues into the diverticula, but the muscular layer is interrupted at the necklike opening of these structures The epithelium is thickly crowded, and on the crests of the folds is arranged tuftlike and in places is much elongated, especially in the diverticula where these cells contain much mucus The lumen of these bronchi is almost filled by mucus in which there are varying numbers of isolated or groups of desquamated ciliated epithelial cells, mononuclear and polymorphonuclear eosinophil cells, Charcot-Leyden's crystals and cellular detritus These constituents are often arranged in twisted thickened lines and arranged in rows The whole bronchial wall is thickened and infiltrated by round cells In the bronchi, from 1 to 3 mm in diameter, the walls are thickened, hyperemic and

thickly infiltrated by round cells, the lymphoid follicles and mucous glands are enlarged, the muscular layer hypertrophic, the diverticula more numerous, and the epithelium single-layered and greatly elongated. The content of the lumen is the same as that in somewhat smaller bronchi. In the chief bronchi mucus exudes from the gland ducts and spreads over the epithelial surface. The hyperemic bronchial glands contain a few fresh epithelioid tubercles.

Comment—The most important points in this case are History of pneumonia at 12 and again at 18, relief from dyspnea after raising masses of mucus, bilateral adhesive pleuritis, complete occlusion of most of middle sized bronchi by mucus, thickening of the bronchial walls, apparent hypertrophy of bronchial musculature, cryptlike structures in the bronchial walls, cellular infiltration, largely eosinophilic, of the bronchial walls, enlargement of the mucous glands and epithelioid tubercles. The history of pneumonia, the bilateral adhesive pleuritis and the cellular infiltration of the bronchial walls all point toward infection as a possible etiology in this case, but an allergic pathogenesis is also indicated by the extensive eosinophilia. The hypertrophy of the musculature is no doubt due to the four years of almost continuous asthmatic attacks of dyspnea. The finding of large mucous glands and of the cryptlike structures in the bronchial walls is significant.

CASE 10 1911 Hermann Heizer¹³ *History*—Child, aged 2 years. Family history negative. Eczema since fourth month. First attack of dyspnea at 9 months. Attacks often followed exposure to wind or dust, and were accompanied by cyanosis, chest noises and the production of a large amount of tenacious sputum. Death followed an attack.

NECROPSY REPORT Macroscopic Examination—Lungs distended. Heart enlarged and right ventricle thickened. Trachea and large bronchi contain a purulent secretion. All lymph glands of the body are greatly enlarged.

Microscopic Examination—The alveoli vary in size, some of their walls are thinned and some are ruptured. Some bronchi are dilated and occluded by masses of mucus containing leukocytes and epithelial cells. The walls of the large bronchi are thickened by infiltrating cells and distended capillaries. The bronchial mucous glands are markedly enlarged and their ducts filled with mucus.

Comment—The most significant findings reported are the history of eczema for months and of attacks following exposure to wind and dust, the generalized enlargement of the lymphoid tissues, hypertrophy of right ventricle, thickening of the walls of the bronchi by cellular infiltration and capillary distension and the occlusion of many bronchi by mucus. The clinical history points to both foods and inhaled dust (animal or plant) as probable etiologic factors in the production of the attacks of dyspnea.

CASE 11 1913 M. M. Tichmeneff¹⁴ *History*—Female, aged 29, college student. No hereditary peculiarities. Nasal catarrh since early childhood. Following an attack of croup in the eighth year, asthmatic attacks lasting from

¹³ Heizer, H. Dissertation, Munchen, 1911.

¹⁴ Tichmeneff. Bronchial Asthma with Death, *Prakt. Vrach* 12:562, 1913.

two to three days came on four or five times each year, usually in the spring and fall, and on two occasions in later years required hospital care. During an attack three weeks before death she entered the hospital with a severe very productive cough, and on examination showed the characteristic posture, difficult whistling expiration, limited excursion, some emphysema, numerous whistling, buzzing râles, normal heart and normal digestive, nervous and urinary systems. Pulse, 112, temperature, 37.5 C. Hemoglobin, 87 per cent, erythrocytes, 5,690,000, leukocytes, 15,200, showing by differential count lymphocytes, 26 per cent, transitionals, 4 per cent, neutrophils, 60 per cent, and eosinophils, 7 per cent. Sputum contained many pus cells, Charcot-Leyden's crystals, Curshmann's spirals and eosinophil cells. Urine contained a trace of albumin. The attack of asthma subsided in three to four days and pneumonic symptoms appeared. Two days before death a severe gastro-intestinal hemorrhage began and continued until death.

Clinical Diagnosis—Bronchial asthma, left-sided exudative pleuritis and pneumonia, ulcer of the stomach or duodenum.

NECROPSY REPORT Macroscopic Examination—The left pleural cavity is partially obliterated by fibrous adhesions and contains 300 c.c. of a purulent exudate. The left upper lobe contains a small cavity and a row of small consolidations from which pus exudes on pressure. The right lung is soft and exudes a mucopurulent fluid. The pericardial sac contains a small amount of clear yellowish fluid. Heart 9 by 9 cm., myocardium pale, large vessels unchanged. Spleen pale and flabby. Liver yellowish. Kidneys pale. Stomach mucosa normal. Large duodenal ulcer 5 cm. from the pylorus showing eroded blood vessels.

Microscopic Examination—Slight brown atrophy of the heart. In the lumen of some of the small bronchi there is an exudate which contains many round cells and leukocytes. The tightly crowded columnar epithelial cells are much elongated and are arranged in several rows as if in increased proliferation. All the layers of the bronchial wall are considerably thickened, due to an increase in connective tissue, round cell infiltration, and hypertrophy of the muscular layer. Some of the bronchi are dilated, their walls markedly infiltrated by round cells, and are surrounded by areas of pneumonic infiltration. The cavity is a typical bronchiectatic cavity.

Comment—The most significant pathologic findings are blood eosinophilia, 7 per cent, adhesive pleuritis and increase in thickness of the bronchial walls due to accumulation of round cells, hypertrophy of muscle layer and increase in connective tissue. This appears to be a true case of bronchial asthma in which death was due to an intestinal hemorrhage. The etiology of the attacks cannot be determined, for the history and the clinical and necropsy evidence point to infection as a possible causal agent, while the eosinophilia points to an allergic pathogenesis.

CASE 12 1916 Marchand¹⁵ *History*—Female, aged 53. Hereditary peculiarities. Mother died of asthma and capillary bronchitis. History of present illness. Capillary bronchitis since 17 and asthmatic attacks since 30. She first entered the hospital in her forty-third year suffering from bronchial asthma, pulmonary emphysema and chronic laryngitis, and left six weeks later much improved. Ten years later, about two weeks before death, she returned to the hospital, following an attack of six weeks' duration, suffering from dyspnea, severe cough with much expectoration, headache, insomnia and

15 Marchand, F. Beitrag zur Pathologie und pathologischen Anatomie des Bronchialasthmas, Beitr. z. path. Anat. u. z. allg. Path. 61:251, 1916.

loss of appetite The attacks came chiefly at night The examination showed a marked dermatographia, cyanosis of the lips and fingers, barrel-shaped chest, labored respiration, lung borders on both sides anteriorly at the seventh rib and posteriorly at the twelfth spinous process, boxy percussion note all over the lungs, deep humming inspiration, prolonged loud, shrill, whistling expiration, heart action accelerated but with tones clear Roentgen-ray examination Diaphragm contracted and with limited motion, distinct hilum shadows, marked pulsation of the right ventricle

She raised a large quantity of a tenacious mucous sputum which contained some spirals, numerous eosinophil cells, but no crystals The blood showed a leukocyte count of 12,600, of which 12 per cent were eosinophil cells Temperature, 37 C The blood serum was very toxic for animals, 0.05 cc causing death of a guinea-pig After standing one and one-half hours, the serum contained many crystals Following a severe attack of two hours' duration, the patient collapsed and died

NECROPSY REPORT *Anatomic Diagnosis*—Severe mucous bronchitis Vesicular emphysema Black circumscribed subpleural indurations in both apices Recent tuberculosis and hypertrophy of the bronchial lymph glands Fibrous induration and calcification of bronchial glands Nodular colloidal goiter Right ventricular hypertrophy and early fatty degeneration of the myocardium Hyperemia of brain Chronic perimetritis Slight atrophic granular kidney Hypertrophy and hyperemia of spleen

Macroscopic Examination—The body is that of a small well-preserved female, weighing 48 kg The tips of the fingers are cyanotic The thorax is not arched The brain shows no signs of disease The diaphragm is at the sixth rib on the right side and in the fifth intercostal space on the left side, and is contracted The lungs do not collapse when the chest is opened, almost completely cover the pericardial sac, and are attached to the chest wall by many stringlike adhesions A fatty remnant of the thymus is present The pericardial sac contains a small amount of a clear yellowish fluid The heart is contracted and the right ventricle appears to be increased in size The valves are slightly thickened The foramen ovale is not completely closed The alveoli in the anterior borders of the lungs are markedly dilated The cross section of the upper lobes are bluish gray and the outer portions are soft and edematous The lower lobes are firmer and filled with blood Most of the smaller bronchi in both upper and lower lobes are completely filled by a tenacious transparent material, which on cross section protrudes and can be drawn out as threads several centimeters long In some places these threads appear as yellowish, opaque masses The larger bronchi contain a more fluid yellowish gray material The lower lobes are fairly dry except for the congested areas Beneath the pleura of both apices there are a few hard black thickenings 1 cm in diameter The mucosa of the trachea, larynx and nasal cavities is not essentially changed

The thyroid is slightly enlarged and contains a small colloid nodule

The bronchial glands are large and soft, the gland at the bifurcation of the trachea being as large as a pigeon egg and containing numerous grayish nodules One gland at the hilum of the right lung contains a calcified nodule

The spleen is enlarged, firm and congested

Microscopic Examination—Blocks of tissue from all parts of the lungs, from bronchial glands, trachea, ethmoid region and the middle turbinate were fixed in liquor formaldehyd, alcohol or Zenker's fluid, and the sections stained with various stains¹⁶

The upper lobes show a vesicular emphysema with the formation of some large vesicles The bronchioli respiratorii are for the most part empty, vary considerably in size up to 0.1 mm and are lined by a low epithelium, some of

16 The detailed descriptions of the sections and of the special form of crystals are omitted in this paper

which is ciliated and measures 0.009 mm. Bronchioli, from 0.5 to 1 mm in diameter, are filled by an homogenous mass containing a few cell elements which is adherent to the epithelium. In some of the smaller bronchioli a transparent, almost homogenous, layer covers the epithelium, the central portion being patent. This layer stains poorly, contains a few mononuclear cells, alveolar epithelium, and shows on high magnification a netlike structure which stains with Weigert's stain like fibrin. The cylindrical epithelium of the smaller, middle-sized bronchioli is mostly intact, and is heaped up and deformed only in the angles between folds. There are no mucous glands present, but the mucumatein stain shows numerous goblet cells in bronchioles 1 mm in diameter. The smaller bronchi contain a longitudinally streaked mucous material, with rows of cells and spirals having distinct central threads. The cellular content of the smaller bronchioles is scanty, while in the larger there are numerous round or elongated polymorphonuclear eosinophil cells which are often arranged in clumps, numerous polymorphonuclear leukocytes, some mononuclear, large, pale, swollen cells (alveolar epithelium), and in the larger bronchioli a few mast cells. In bronchioli, from 0.5 to 0.8 mm in diameter, the epithelium varies in thickness from 0.025 to 0.04 mm, and in bronchi from 3.5 to 4 mm in diameter, it varies from 0.05 to 0.06 mm in thickness. The content of the larger bronchi and the trachea is composed of much well-preserved ciliated epithelium, many large markedly swollen round cells which contain droplets of myelin material, granular cells resembling eosinophil cells, a few Charcot-Leyden's crystals and numerous crystals which are different from the Charcot-Leyden's crystals. The trachea also contains several clumps of bacteria, most of which resemble the influenza bacillus. The epithelium of the larger bronchi and the trachea contains numerous goblet cells and is infiltrated by a few leukocytes, eosinophil cells and mast cells. The nasal mucosa over the free borders of the turbinates is thickened and infiltrated by cells.

The walls of all the bronchioles are more or less infiltrated by round cells of different kinds, the lymphoid elements being most numerous and often grouped to form small nodules under the epithelium and in the outer layer. The other kinds of cells, which frequently separate the muscle bundles, are (a) large mononuclear basophilic cells often grouped around the acini of mucous glands, (b) eosinophils, (c) mast cells varying greatly in size and lying chiefly close to the epithelium, (d) a few polymorphonuclear leukocytes.

The mucous glands of the larger bronchi and the trachea show a more or less active secretion with transformation of the cylindrical cells of the duct into goblet cells. The gland cells are for the greater part markedly swollen and filled with mucus.

The blood smears and rib-marrow preparations contained numerous eosinophil cells, while the spleen contained only a few such cells. The lymph glands at the bifurcation of the trachea are enlarged and contain a small tubercle with some caseation and giant cells.

Comment—The most important pathologic findings are complete occlusion of most of the smaller bronchi, cellular infiltration in the bronchial wall, enlargement of the bronchial mucous glands and the numerous eosinophil cells in the bronchial wall. The history of bronchitis since the seventeenth year and of asthma beginning in the thirtieth year, the necropsy finding of marked cellular infiltration of the bronchial walls, point to infection as a probable etiologic factor in this case, but the eosinophilia indicates an allergic pathogenesis.

CASE 13 1916 Marchand¹⁵ *History*—Mrs. T. B., aged 45. Previous history. The patient has had two severe attacks of asthma in the year preceding her entrance into the hospital where she had a third fatal attack.

NECROPSY REPORT *Anatomic Diagnosis*—Marked fibrinous bronchitis with obturation of the left bronchus, fibrinomucous tracheitis, purulent bronchiolitis, marked pulmonary emphysema, healed right apical tuberculosis, fibrinous lobular pneumonia, cyanosis of the liver, spleen and kidney, small hemangioma of the liver, accessory spleen in tail of pancreas

Macroscopic Examination—Small emaciated woman with scanty fatty and muscular tissues. Diaphragm on right side at fourth rib and on left at fourth interspace. Heart not enlarged. Left ventricle, 8 mm and the right 3 mm in thickness.

The lungs do not collapse when the chest is opened. There are a few adhesions to the sternum. Both lungs are large and light. The posterior portion of the right upper lobe contains a few hazelnut-sized areas with caseous centers. On cut section the lung tissue is dry and contains little blood. The left chief bronchus and its branches are almost completely occluded by a tenacious exudate. The middle-sized bronchi contain glassy tenacious mucus and the finer branches contain a more fluid yellowish turbid exudate. The mucosa of the chief and smaller bronchi is swollen and reddish. The trachea contains an adherent mucous mass which extends into the right main bronchus. The peritracheal and peribronchial lymph glands are enlarged and contain no nodules. The liver extends two fingers below the costal margin. The spleen is not enlarged.

Microscopic Examination—The lungs were fixed in liquor formaldehyd and preserved in alcohol. A large number of blocks of completely infiltrated and air-filled portions of the tissue were taken, but the original positions of these blocks could not be established later. The cross section of the exudate filled bronchi appears as whitish round disks in both the infiltrated and air-containing portions. The parenchyma of the infiltrated portions of lung resembles a catarrhal lobular pneumonia and contains many polymorphonuclear neutrophil cells, but no eosinophil cells. The parenchyma of the air-containing portions shows a moderate degree of emphysema.

The content of the lumen of the small and middle-sized bronchi in both air-containing and infiltrated portions is made up of homogenous, transparent mucus which has in many places a streaked appearance and which contains many closely crowded polymorphonuclear neutrophil cells but no eosinophils. The cylindrical epithelium is fairly well retained and contains a few globule cells. The walls of the bronchi are thickened and contain, especially in the outer layer and between muscle bundles, many mononuclear lymphoid cells, although the blood-filled vessels contain no cells of this type and show no evidence of their migration. In some of these bronchi there are numerous eosinophil cells, either rowlike, scattered or clumped between connective tissue bundles, and most numerous in the inner layers. The eosinophil cells also intermingle with the lymphoid cells in the outer portion of the lymph nodules. There is no definite relation between accumulations of eosinophil cells and the blood vessels. These cells vary in shape and size, in number, distribution, intensity of staining property and size of granules, and in morphology and size of the nucleus. All transitions of nuclei from the mononuclear to the polymorphonuclear are visible. There are no Charcot-Leyden's crystals among the eosinophil cells or in the bronchial wall.

The lumina of some of the larger bronchi, as shown in pictures, are completely occluded by a transparent exudate which is adherent to the wall and is continuous with the content of the gland ducts. The epithelium is partially desquamated and in places necrotic. The tissue of the walls is markedly infiltrated by cells, chiefly polymorphonuclear neutrophils and eosinophils. The latter predominate in some portions of the wall, and with the neutrophils are seen penetrating the hyalin tunica propria. A few Charcot-Leyden's crystals also are present. The blood vessels are engorged with erythrocytes, among which there are a few mononuclear and polymorphonuclear leukocytes, none being eosinophilic. The cells of numerous large mucous glands in the wall are

distended by mucus, as are also many of the duct cells. In some portions of the wall there are circumscribed or diffuse collections of lymphocytic cells.

The left chief bronchus from 1 to 3 cm from the bifurcation is almost occluded by an exudate and its epithelium partially desquamated. The mucous gland ducts are filled by mucus and the cells of the ducts and acini are distended. The mucosa is markedly infiltrated by round cells, partly mononuclear and partly polymorphonuclear, and many eosinophil cells. Some Charcot-Leyden's crystals are present in the walls and on the surface of the mucosa. The content of the lumen is composed of mucus and fibrin which show a spiral arrangement. In some places well-formed spirals with central threads are seen.

Many eosinophil cells and Charcot-Leyden's crystals are found in the mucosa of the trachea. In some of the thin paraffin sections small groups of organisms resembling the diphtheria bacillus are seen.

Comment—The most significant findings in this case are (1) The complete occlusion of many of the larger, middle sized and smaller bronchi by mucous masses. (2) Marked cellular infiltration of the walls of the bronchi. (3) Presence of eosinophil cells, scattered or grouped, in the walls of the trachea and some of the bronchi. (4) Presence of Charcot-Leyden's crystals in the walls of the trachea and in some of the bronchi. (5) Distension of the cells of the mucous glands and their ducts by mucus.

The etiology of the asthmatic attacks in this case has not been determined. The history of the asthmatic attacks coming on in the last year of life in a person 45 years of age, and the evidence of infection in the walls of the bronchi, point to bacteria as probable factors in the production of the attacks, but the extensive eosinophilic infiltration of the bronchi points again to an allergic pathogenesis.

CASE 14 1918 Marchand¹⁷ *History*—Male, aged 48, worker in chemical factory. Family history. Aunt had asthma. Previous illnesses. None. When about 44 years of age he began work in a chemical factory and frequently inhaled poisonous fumes. Before quitting this work, two years later, he had his first attack of asthma after exposure to fumes. After this he often had marked dyspnea on exertion and his work was interrupted frequently, the dyspnea being always more noticeable in damp weather. After a free period during the following summer the attacks returned, accompanied by cough with the raising of a tenacious mucus, and the patient was often compelled to remain in bed for several days. About ten weeks before death both legs began to swell and he entered the hospital with the following findings. Edema and cyanosis of face, high grade inspiratory dyspnea, prolonged whistling expiration, lung lowered and immovable, heart and abdomen negative, sputum scanty, tenacious and containing crystals and eosinophils, urine negative. The blood was examined several times during the stay in the hospital and showed an eosinophilia averaging about 4 per cent. The blood pressure ranged from 135 systolic and 85 diastolic on entrance to 86 systolic and 60 diastolic two weeks before death. The patient's condition gradually became worse and about nine weeks after entrance, he died.

NECROPSY REPORT *Anatomic Diagnosis*—Catarrh of the bronchial mucosa, catarrhal rhinitis with retained mucus in the left maxillary sinus, diffuse

17 Marchand, F. Ein neuer Fall von Asthma Bronchiale mit anatomischer Untersuchung, *Deutsch Arch f klin Med* 127 184, 1918.

vesicular pulmonary emphysema, slight hypertrophy of the right ventricle, bronchial asthma

Macroscopic Examination—The lower part of the thorax is widened. The lungs are expanded and cover the heart. The bronchi up to the smaller branches are filled by yellowish-white tough masses which can be pulled out like threads. The left antrum of Highmore is completely filled by a tough opaque bluish secretion. The bronchial glands are not enlarged. The right auricle and ventricle are dilated and the walls thickened.

Microscopic Examination—The mucous membrane of the nasal septum, turbinates and trachea contains many distended capillaries and is infiltrated by round cells, many of which are eosinophilic. The fresh secretions from the trachea and principal bronchi contain many prismatic crystals similar to those described in a previous case (Case 12 Marchand's first case). The lumen of the bronchi 5 mm in diameter contains only a small amount of mucus in which are desquamated cells, leukocytes, round cells and a few eosinophils. The epithelium is mostly desquamated. The mucosa is unevenly thickened, its capillaries engorged and all layers contain numerous eosinophil cells which are often arranged in masses near the hypertrophied muscle layer. The mucous gland cells are swollen and contain no eosinophil cells. Smaller bronchi have a similar structure and are filled with mucous masses which have typical spiral arrangement. The smallest bronchioles and the alveoli are not essentially changed. One lymph gland contains a small tubercle.

Comment—The most important points in this case are the complete occlusion of many smaller bronchi, enlargement of the mucous glands, hypertrophy of the muscle layer and the large number of eosinophilic cells infiltrating the bronchial walls.

CASE 15 1921 N Kamchorn and A G Ellis¹⁸ Male Siamese, actor and fishmonger, aged 52. Family history of asthma in four generations. Father's mother, father, one uncle, one aunt, and one child. Infrequent asthmatic attacks began in childhood and gradually became more frequent. Three months before admission to the hospital the feet and legs began to swell. On entrance eleven days before death, there was a marked edema, cyanosis and respiratory dyspnea. Coughing produced a tough white sputum. The heart sounds were faint and râles were heard over the bases of both lungs. Treatment gave no relief and death resulted from failure of the heart.

NECROPSY REPORT *Anatomic Diagnosis*—Summary. Hypertrophy and dilatation of right ventricle, dilatation of right auricle and left ventricle, bilateral chronic adhesive pleuritis, partial atelectasis of left lung and lower lobe of right lung, vesicular and interstitial emphysema of right upper and middle lobes, acute bronchitis of left lung and right lower lobe, congestion of spleen, kidneys, stomach and liver, anasarca, multiple serous effusions.

Macroscopic Examination—Body edematous. All serous cavities, except the obliterated left pleural sac, contain much fluid. The right ventricular wall is 1 cm thick. The left lung and the right lower lobe are collapsed and their cut surfaces are dark bluish red in color. The middle sized and smaller bronchi contain a moderate amount of tenacious mucus and the mucosa is intensely red. The right upper and middle lobes are overdistended but on pressure and on incision exude frothy serum. The bronchi in these lobes are empty and the mucosa is pale in color.

Microscopic Examination—The bronchial exudate contains much mucus, typical Curshmann's spirals, columnar epithelial cells and an occasional eosinophil cell. The epithelium of the bronchioles in the collapsed portion of the lungs is desquamated and its place occupied by polynuclear and mononuclear leuko-

18 Kamchorn, N., and Ellis, A G. *Am J M Sc* 161 525, 1921

cytes The bronchial walls are infiltrated by mononuclear cells The epithelium of the middle sized bronchi is partially desquamated There is no evidence of increased fibrous tissue and of thickening of the bronchial wall and the muscularis mucosa does not appear abnormal The bronchi in the distended portions of the lung have much less marked changes

Comment—The following points are the most important in this case The history of asthmatic attacks since childhood and the microscopic evidence of an extensive respiratory infection sometime during life, as shown by the extensive round cell infiltration of the subepithelial layer of the bronchial tree The hypertrophy of the wall of the right ventricle is probably due to the extra load thrown on pulmonic circulation during attacks The remaining pathology in this case is probably dependent on the failing heart

MODE OF PROCEDURE EMPLOYED IN THIS STUDY AND A DESCRIPTION OF THE NORMAL BRONCHIAL STRUCTURES

Before discussing in detail the various changes involving some of the different structures which may be implicated in the production of bronchial stenosis, i e, the smooth muscle fiber system, the mucosa, the glandular system, the blood vessels and lymphatics and the nerves, we deem it proper to give a brief description of the finer anatomy of the normal bronchial structures¹⁹

When possible, in all cases studied, the intact lung was fixed either in liquor formaldehyd or in Zenker's fixing fluid, and each lobe was sectioned as described so that the blocks of tissue gave either cross or longitudinal views of the main branching of the bronchial tree from the hilum to the pleural surface (Fig 1) The cross sections for microscopic study were taken as nearly as possible from the plane at right angles to the central axis, as it is clearly seen that sections through oblique planes must give a distorted picture of the structures The sections were stained with hemotoxylin and eosin and Van Gieson's and Mallory's connective tissue stains

We have examined microscopically the lungs of several persons which should have shown, according to the history and the macroscopic examination, practically normal structures, yet we have found in all of them some pathologic changes, i e, foci of round cell infiltration, tubercles, calcified cartilages, capillary dilatation or other changes

¹⁹ Oppel Lehrbuch der vergleichenden mikroskopischen Anatomie 6-7. Miller, W S Reference Handbook Medical Sciences, Am Rev Tuberc 2. (May) 1918, 2 (Jan) 1919, Anat Rec 5 (March) 1911, Bull Robert Koch Soc for Study of Tuberc (Feb 11) 1913, (April 20) 1916, Anat Anz 28 1906, Contributions to Embryology, No 38 Larsell, O Nerve Terminations in the Lung of the Rabbit, J Compar Neurol 33 105, 1921 Baltisberger, W Ueber die glatte Muskulatur der Menschlichen Lunge, Ztschr f Anat in Entwicklungsgeschichte 61 249, 1921

which distorted the normal picture in some particular. These findings, in accordance with similar reports from others, show that few of us escape the marks left by acute or chronic respiratory infections which are capable of altering the normal tissue.

The principal bronchi enter the hilum of the lung and divide and subdivide quickly several times into smaller tubes, which when they are reduced in size to from 0.5 mm to 1 mm inside diameter, are termed bronchioles. These bronchioles divide to form the atrium, air sac (infundibulum), and the air cell (alveolus).

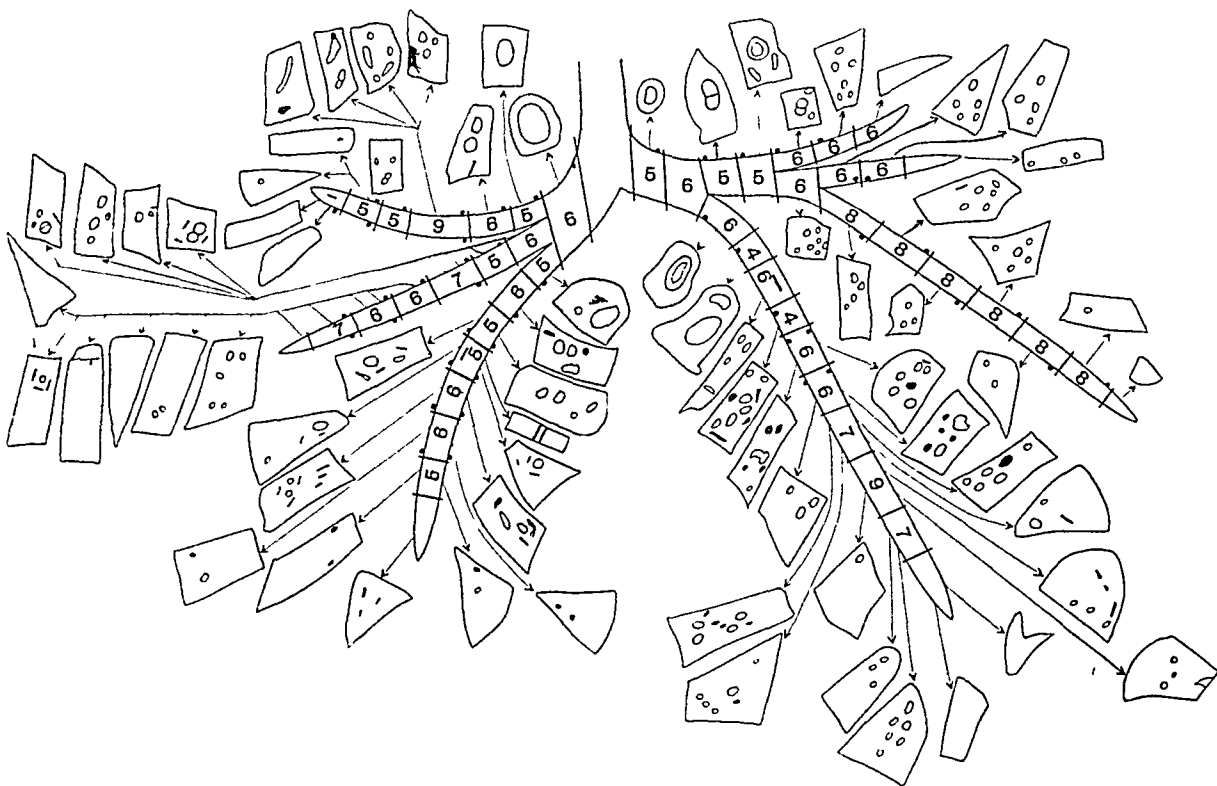


Fig 1—Diagram showing the method used for obtaining the blocks of lung tissue which contain the parts of the bronchial tree studied. The figures give the actual thickness in millimeters of the blocks used. The black dots along the bronchial margin indicate the side of the block from which the sections were taken for study. The measurements and sections shown in this diagram correspond to those actually obtained in Case 6.

The structure of all these divisions is, in general, the same, the arrangement, diminution or disappearance of any layer being incidental to the reduction in the size of the tube. We shall discuss briefly the following structures. The epithelium, basement membrane, sub-epithelial tissue, muscle, mucous glands and the outer fibrocartilaginous layer.

Epithelium—The epithelium in the trachea and larger bronchi is made up of two or three layers, a deep layer of small, closely approxi-

mated cells, which in places has the appearance of two layers of cells, and a lining layer of ciliated columnar cells from which processes extend and attach to the basement membrane. In this lining layer there are also the goblet cells, which are most numerous in the larger bronchi and gradually disappear as the size of the tube decreases, but may be found even in the bronchioles. The epithelium also gradually changes in character from the layered ciliated type in the large bronchi to the single layer of ciliated or nonciliated cuboidal cells or flat cells in the bronchiole. This epithelium throughout is thrown into shallow longitudinal folds.

Basement Membrane—The well-marked basement membrane on which the epithelium rests forms a thin compact layer, containing a few spindle shaped cells, and is pierced here and there by gland ducts and by processes passing into the epithelium.

Subepithelial Tissue—The layer of loose connective tissue which is found just beneath the epithelium in all the divisions of the bronchi down to the bronchiole, has been designated by us the subepithelial connective tissue layer. It contains numerous capillaries, fine elastic fibers, small round cells and connective tissue cells and intermingles in its outer portion with the coarser elastic fiber layer. This latter layer is prominent in all the divisions of the bronchi down to and including the bronchioles, forming distinct longitudinal bundles of fibers which show some irregularities in the direction where gland ducts, vessels, etc., penetrate it. In these places the fibers may appear to form distinct circular bundles.

Muscle—The description of the nonstriated muscular system of the bronchial tree and the lung parenchyma in histologies, almost without exception, is very meagre and misleading, and few observers, who have made no special study of this system, appreciate its complicated structure, extent and importance. In the trachea and in the main bronchi with similar structure, the muscle tissue is practically limited to the posterior membranous part where it forms bundles that extend between the ends of the incomplete ring cartilages and the interval between them, but, when these cartilages are replaced by irregular plates in the further divisions of the bronchi, the muscle forms a more or less continuous layer, the so-called "ring muscle" layer. The fact is, that, in man at least, this layer is not a true ring muscle, except probably in the finer bronchi, but is made up of short bundles which join each other in such a manner that a netlike sheath encircling the tube is formed, the general direction of the fibers being circular. As the tube diminishes in size, the muscular layer becomes thinner and thinner, and in the respiratory bronchiole and in the lung parenchyma it is represented by only a few delicate fibers. In certain lower animals, e. g., the turtle,

the distribution of smooth muscle fibers in the lung parenchyma is very striking

The layer which connects the muscularis to the fibrocartilaginous layer consists of areolar tissue and contains mucous glands and mucoserous glands, blood vessels, nerves, and adipose tissue. This layer is best developed in the larger bronchi and, as the size of the tube diminishes, becomes progressively thinner, the glands being rarely found in tubes less than 1 mm inside diameter.

Glands—The gland system, like the muscle system, has not received the attention of the histologist that it deserves. The glands are of the tubulo-alveolar variety and are distributed chiefly between the cartilages and the muscle layer about the whole circumference of the bronchus, but in middle sized and smaller bronchi they are best developed in the tissue between the edges of the cartilage plaques and may even appear outside the cartilages. They are chiefly mucous glands but contain also a few crescents of Gianuzzi. The acini are lined by columnar epithelium and the ducts which often form ampullae-like widenings on entering the mucosa are lined by cuboidal ciliated epithelial cells. In certain animals, especially in rodents, gland tissue is absent in all the bronchial divisions within the lung. In others where glands are present the proportion of mucous to serous gland tissue varies greatly, thus in the sheep and the dog the serous glands are in preponderance while in cattle the amounts of serous and of mucous gland tissue are about equal.

Fibrocartilage Layer—The outer layer of the bronchial tree is composed chiefly of connective tissue which in all except the finer divisions of the bronchi contains cartilages. These cartilages in the trachea and the primary bronchi form incomplete rings extending over the ventral and lateral walls, but in further divisions of the tube are broken up into irregularly shaped plates of various sizes and are disposed over the whole circumference of the tube. These plates gradually diminish in size and number and are rarely present in tubes with an inside diameter of less than 1 mm. The connective tissue, however, continues as a distinct layer into the much smaller divisions. It is interesting to note here that cartilages are absent in that portion of the bronchial tree within the lungs of some small animals, chiefly rodents.

Lymphoid Tissue—This is found in all the main branchings of the bronchial tree, the amount varying according to the size of the tube. There are a few scattered cells of the lymphoid type in the subepithelial layer but true follicles and nodes are found only outside the muscular layer. Here these structures may lie between the muscle and cartilages, in the tissue between the cartilages, or as is usual for distinct nodes, outside the cartilages. The distinct nodes are usually located at the

point of bifurcation of the tube. Small lymphoid follicles are also found scattered in the wall of small bronchioles and even among the alveoli or beneath the pleura. Distinct glands are found about the trachea and larger division of the bronchi.

Blood Supply—The blood supply of the bronchial tree is furnished by a special set of vessels, the bronchial arteries, branches of which are found in all the divisions of the bronchus down to the bronchiole. The main branches of this artery are situated in the outer fibrous coat of the bronchus, numerous radicles being given off to form plexuses which supply blood to the glands, muscles and other structures, the capillary network being especially rich in the subepithelial layer.

Nerves—Nerves and nerve ganglia are found in the walls of all divisions of the bronchial tree down to the bronchiole, usually lying in close apposition to the branches of the bronchial artery.

REPORT OF CASES

CASE 1—Mrs. B., aged 55, married, American, was first seen by one of us (K.) in April, 1915, suffering from frequent severe attacks of spasmodic dyspnea.

Family History—Negative.

Precious History—At 44 she had had a severe tonsillitis and one attack of severe abdominal pain (appendicitis?), but after that time she was well until April, 1913, when she suffered from an acute coryza and severe cough lasting three weeks. During the following summer (1913) she was very nervous and irritable, and in August she went to the White Mountains. Then she first noticed wheezing sounds in the chest at night. During the latter part of August and in September she had frequent head colds accompanied by severe coughing attacks, and in the latter part of September, following a severe prolonged coughing spell, the first distinct attack of spasmodic dyspnea occurred. These attacks of coughing and dyspnea increased rapidly in number and severity, and by October 10 they were coming four and five times daily, but were usually almost instantly relieved by small subcutaneous doses of epinephrin (1/1000). While visiting in the South in November and December she had complete relief from dyspneic attacks but the severe cough persisted, although usually relieved quickly by inhaling the smoke of stramonium leaves. While returning North in January, 1914, she contracted a severe cold and the dyspneic attacks returned with increased severity, forcing her to stop off at Atlanta, Ga., where she remained under a physician's care for about three months, apparently suffering from a bronchopneumonia. In April, in Chicago, the paroxysmal attacks of dyspnea again returned with increased frequency and severity and were incompletely relieved by subcutaneous injections of epinephrin, but the troublesome cough was relieved by small doses of potassium iodid. The attacks of dyspnea and coughing persisted to a greater or lesser degree all summer while traveling in the West. In September, 1914, she entered a Chicago hospital for observation by a local internist. There a tooth infection was cleaned up and a vaccine, made from her sputum cultures, was administered, but these measures seemed to give only a transient relief of symptoms. Following a pneumococcus infection in February, 1915, with a rise in temperature, she had almost complete relief from both the dyspneic attacks and the harassing cough until the latter part of March, when both returned in a severe form. At this time she entered the Presbyterian Hospital in Chicago.

Laboratory Examination—Temperature, 98.6 F, pulse, 96, respiration, 24
Blood pressure, 115/75

Blood Hemoglobin, 95 per cent, leukocytes, 14,000, red cells, 5,700,000
Differential count Small lymphocytes, 10 per cent, large lymphocytes, 10 per cent, large mononuclears, 5 per cent, transitionals, 2 per cent, neutrophils, 62 per cent, eosinophils, 11 per cent

Urine Acid, specific gravity, 1.020, no albumin, sugar, acetone, or casts, few leukocytes, no blood, indican, a trace

Sputum Very abundantly produced, thick, mucoid, stringy with white particles, no Charcot-Leyden crystals, Curshmann's spirals or blood, a few eosinophils, but no polymorphonuclear neutrophil leukocytes

Feces Negative for blood and pus

Physical Examination—Skin, pale and dry, with cyanotic hue of the lips, nose, fingers and nails No palpable glands Throat, nose and sinuses negative (Dr Shambaugh) Teeth negative (Dr Moorehead) Chest Increased in anteroposterior diameter Intercostal spaces widened Posture (sitting in bed) stooped Lower lung borders anteriorly in midclavicular line at the seventh intercostal space, posteriorly, at the level of the twelfth spinous process Excursion on deepest inspiration scarcely one-half inch Vocal fremitus not increased Percussion note hyperresonant over both lungs Both inspiratory and expiratory phases markedly prolonged Sonorous and sibilant râles over whole chest Heart Apex beat not visible or palpable Epigastric pulsation present Heart borders not determinable All heart sounds soft and feeble but clear No murmurs Liver Easily palpable and extends about 2 cm below costal arch Spleen Palpable No masses in the abdomen Sputum Bacteriologic examination done at several periods of her stay in the hospital showed aerobic *Streptococcus viridans*, *Micrococcus catenalis* and *pneumococcus* Anaerobic *Bacillus annuliformis*, *Streptococcus parvus*, *Bacillus fusiformis*

Treatment and Course—Epinephrin, atropin, potassium iodid and strong coffee gave symptomatic relief of short duration The administration of autogenous vaccines was followed by short periods of improvement This, however, was not permanent and the recurrence of several paroxysms of dyspnea depressed the patient to such a degree of despondency that she sought and found a voluntary death through drowning The body was in the water about three hours and was examined five hours after death

Macroscopic Examination—Not obtainable (Coroner's case)

Microscopic Examination—The pleurae of both lungs vary in thickness and contain but a few foci of round cells Most of the alveoli are of normal size, contain only an occasional endothelial cell, and have thin walls which also contain a few small foci of round cells In the outer borders of both lungs the alveoli are dilated and some have ruptured walls One small group of alveoli in the right lower lobe contains a fine granular precipitate in which there are numerous polymorphonuclear neutrophilic leukocytes The ductuli respiratorii are patent, slightly dilated and their walls without appreciable change The bronchioles, even to the smallest, are somewhat dilated and most of them are occluded by homogenous mucous masses which contain a few epithelial cells, round cells and many polymorphonuclear cells, many of which are eosinophilic The walls are thin because of the dilatation, contain only a few round cells and have thin strands of smooth muscle fibers and of elastic tissue The epithelium is only partially retained and in all except the smallest bronchioles it rests on a very prominent hyalinized basement membrane Many bronchioli are dilated to such a degree that they can be differentiated from small bronchi only by their structure

The small and middle sized bronchi are dilated so that longitudinal folds are obliterated, and almost all are occluded by mucous masses which vary somewhat in structure and constituents In some, the mass is homogenous

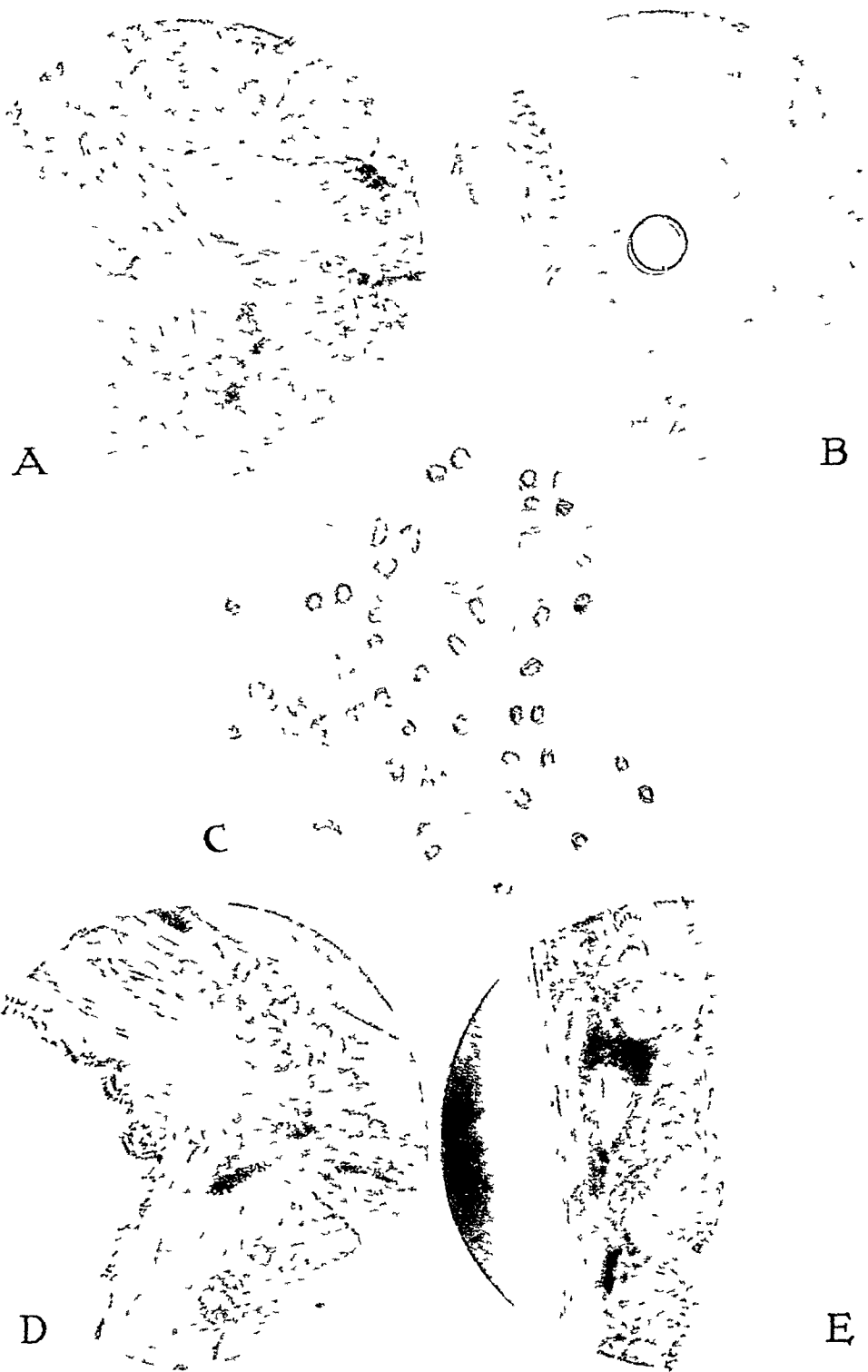


PLATE 1

Plate 1—Bacterial-type of asthma Case 1 A Cross section of a large bronchus Note the muscle bundles, basement membrane, marked hypertrophy of mucous glands, and cellular infiltration

B Longitudinal section of a large bronchus Note the muscle bundles, cellular infiltration, mucous glands, and eosinophil cells High magnification of the area marked by the circle is shown in C

C High magnification of the area marked by the circle in B

D Bacterial type of asthma Case 2 Cross section of a large bronchus Note the muscle bundles, mucous glands, and distended capillaries

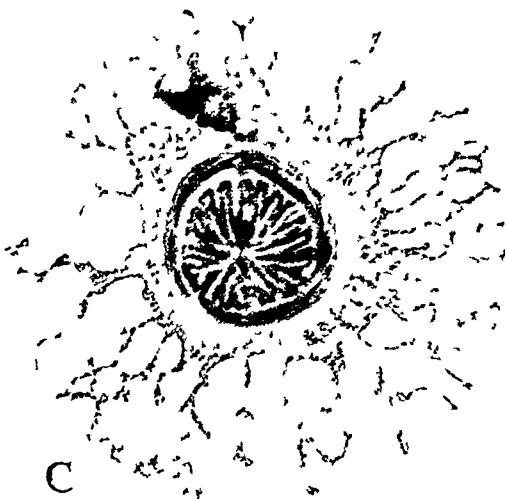
E Longitudinal section of a large bronchus Note the muscle bundles, distended capillaries and cellular infiltration



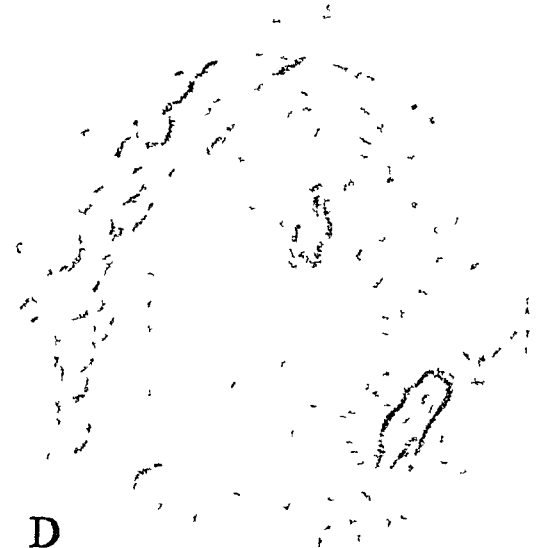
A



B



C



D

PLATE 2

Plate 2—Bacterial type of asthma Case 2 A Bronchiole almost occluded by a folding of the epithelium

B Case 3 Bronchiole occluded by folds of epithelium

C Bronchiole of a guinea-pig Fatal horse serum anaphylaxis

D Food asthma Case 6 Area of absorption atelectasis with an adjoining area of normal lung tissue

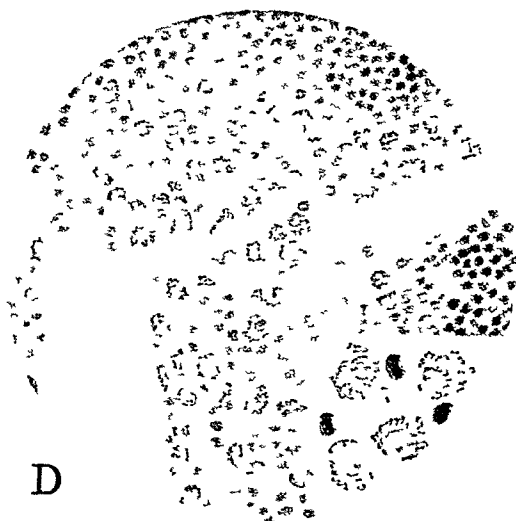
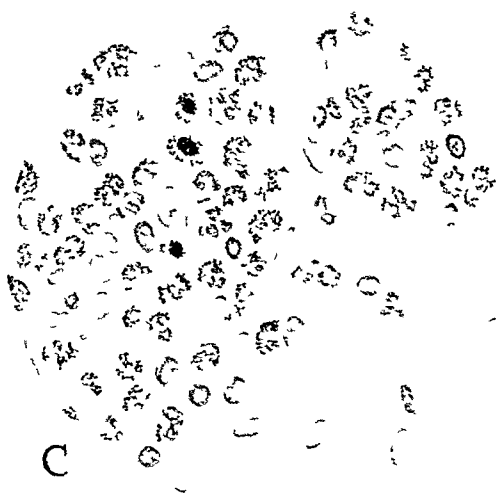
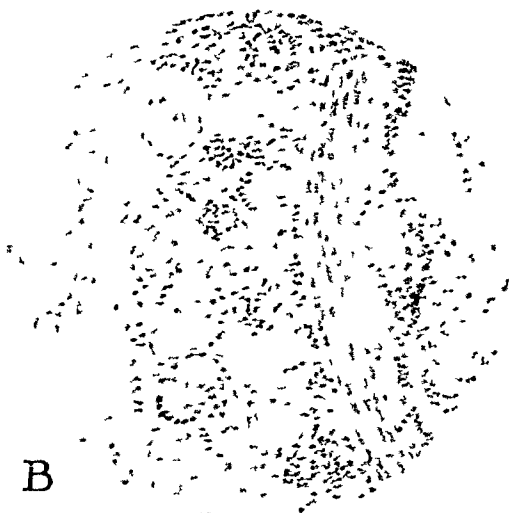
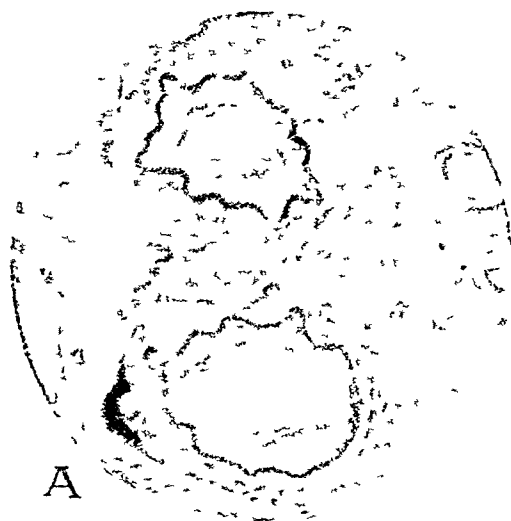


PLATE 3

- Plate 3—Food asthma Case 6 A Occlusion of bronchi by mucous exudate
 B Cross section of a large bronchus Note the muscle bundles, distended capillaries and extensive infiltration by eosinophil cells
 C High magnification of an area of eosinophilic infiltration in the bronchial wall
 D Mononuclear eosinophil cells in the thymus Insert a high magnification of these cells

and contains diffusely scattered and polymorphonuclear cells which are mostly eosinophilic, some round cells and near the outer zone desquamated epithelial cells. In others, the mass appears much twisted, having whorllike thickened lines and rows of cells intermingled with layers of homogeneous cell free mucus. In many bronchi the mucous masses appear to be flowing stream-like into the bronchi from the gland ducts. No fibrin and only a few erythrocytes are found. The epithelium is for the most part desquamated, only the lower layer of small cells remaining attached to the thickened prominent basement membrane. The basement membrane is conspicuous and extends as a prominent band up into the gland ducts, at times even up to the gland itself. The subepithelial layer contains many cells chiefly small round cells, a few eosinophil cells, mostly polymorphonuclear, and a few mast cells. The elastic tissue is prominent in some bronchi and in all, the capillaries are numerous but small. The muscle tissue varies greatly in thickness, being prominent in all bronchi but in some forming large bundles which are best seen in the longitudinal sections (Fig 2). There is no evidence of hyaline degeneration or fatty infiltration of the muscle. The mucous glands are very large and many are densely infiltrated by cells (Fig 3). In most the acini are large, filled by mucus and are often separated widely by infiltrating cells which obscure large portions of the gland structure. These cells are mostly small round cells, but in some glands the predominating cells are polymorphonuclear eosinophil cells. Some glands are almost completely destroyed by this infiltration. The gland ducts leading from these glands are large and in many places distinct ampullae are formed which contain mucus or mucus inclosing many cells. Many of the ducts are surrounded by a zone of round cells (Plate 1, A, B, C). Some of the cartilaginous plaques in both lungs show small areas of calcification. The walls of some of the bronchial arteries are thickened. No nerves or nerve ganglia are invaded by round cells.

The structure of the larger bronchi is similar to that of the smaller bronchi except that the mucus does not completely occlude any of them. No Charcot-Leyden's crystals or Curshmann's spirals are found, and although the epithelium is missing throughout, no evidence of true ulceration can be demonstrated.

The bronchial lymph glands of both lungs are large and anthracotic, their sinuses contain a few polymorphonuclear eosinophils and they contain no evidence of tuberculosis.

Summary—The most significant pulmonary pathologic findings in this case are (1) Complete occlusion of the majority of the middle sized and small bronchi and of the bronchioles by a mucous cellular exudate. (2) Numerous large mucus-filled gland-duct ampullae (Schleimhautausstülpungen of Monckeberg). (3) Large active mucous glands. (4) Marked cellular infiltration of the subepithelial layer and of the mucous glands. (5) Prominence of the basement membrane and of the muscular layer. (6) Tissue eosinophilia.

Comment—The history of previous attacks of bronchitis and of pneumonia, of asthmatic attacks beginning after the fiftieth year, and the microscopic evidence of infection in the bronchial walls point to bacteria as the causal agent in this case of asthma.

CASE 2—Mr G, aged 55, married, American, entered the Presbyterian Hospital, July, 1917, under the care of one of us (K).

History—Except for having had the usual diseases of childhood, he was exceptionally well until his forty-ninth summer (1911), when a severe bronchitis developed and persisted for six months, being accompanied near the end by wheezing sounds and one definite attack of spasmodic dyspnea. The following spring he had a second attack of bronchitis accompanied by wheezing sounds and one attack of spasmodic dyspnea. Following this the attacks

came more frequently each year so that, at the time of entrance into the hospital, six years after the first attack, they occurred as frequently as from three to five times daily with only short periods of freedom. During this time (six years) the weight gradually fell from 155 to 90 pounds. Tobacco and alcohol never used. Gonorrhea and syphilis denied.

During the three years prior to July, 1917, the following surgical and medical procedures were instituted without giving relief: 1914 Nasal polyp removed. 1915 Twenty injections of a stock vaccine. Potassium iodid up to 50 minims, three times daily. Teeth were roentgenographed and two were removed. Polyp and turbinates removed. 1916 Tonsils removed. Eleven injections of arsphenamin (negative blood Wassermann¹). 1917 Use of mixed

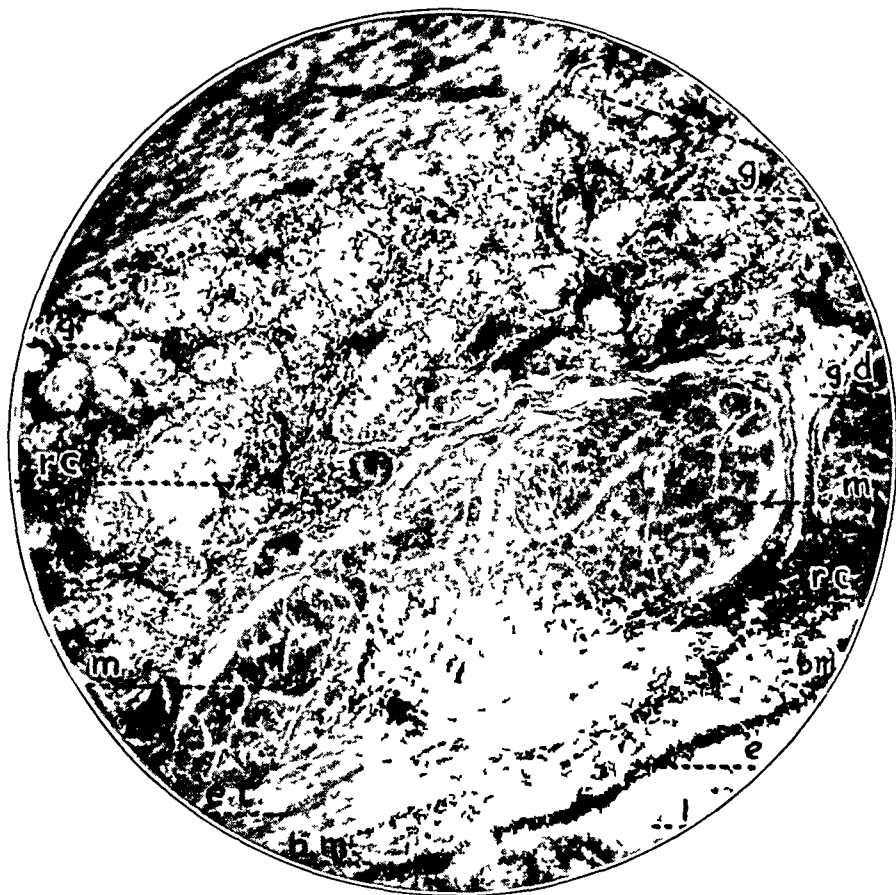


Fig 2 Case 1 Bacterial asthma. Large bronchus. Longitudinal section. Epithelium intact. Basement membrane thick and hyalinized. Subepithelial layer infiltrated by round cells. Muscle bundles very large. Glands have distended acini and contain foci of round cells. *l*=lumen, *e*=epithelium; *bm*=basement membrane, *et*=elastic tissue, *rc*=round cells, *m*=muscle, *gd*=gland duct, *g*=gland. Magnification, 65 diameters.

vaccine. Removal of colon was advised by family physician as roentgen-ray examination showed a vicerptosis, especially marked of the transverse colon. The patient had noted that frequent catharsis and use of enemas seemed to alleviate the attacks.

Family History—Mother, two sisters, one brother, and one child have had asthma.

Physical Examination—At the time of entrance into the hospital in the summer of 1917, the following observations were made. Small, much emaciated

man Head and neck, negative Chest thin walled, expansion fair, numerous squeaky and whistling râles on both sides Heart Left border 10 cm from midsternal line Rate, tone and rhythm appear normal Abdomen Wall muscular Small umbilical hernia Liver Palpable 2 cm below costal margin in midclavicular line Spleen Not palpable Inguinal glands Easily palpable Extremities Negative

Blood Hemoglobin, 75 per cent, leukocytes, 7,900, red cells, 3,670,000 Differential count Small lymphocytes, 23 per cent, large lymphocytes, 8 per cent, polymorphonuclear neutrophils, 59 per cent, polymorphonuclear eosinophils, 10 per cent

Urine Specific gravity, 1.032, no albumin, casts, sugar or pus

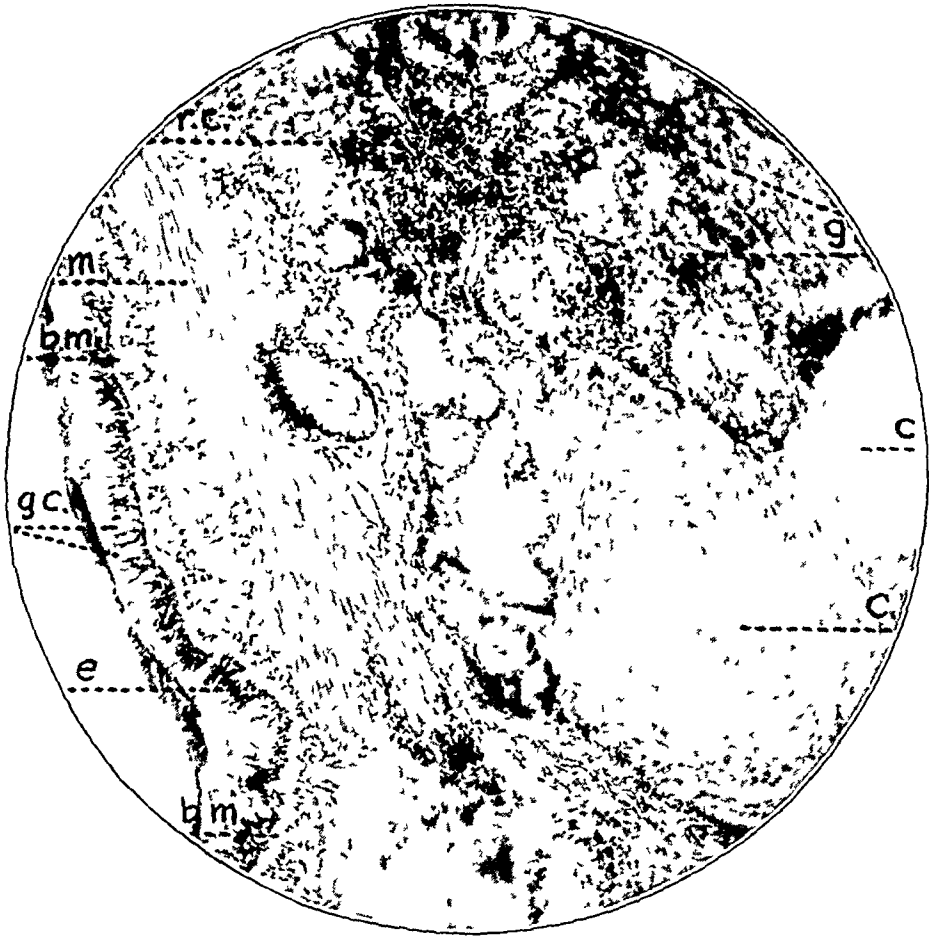


Fig 3 Case 1 Bacterial asthma Large bronchus Cross section Epithelium intact and containing goblet cells Basement membrane thick and hyalinized Subepithelial layer infiltrated by round cells Muscle bundles large Mucous glands large and infiltrated by round cells *e* = epithelium, *gc* = goblet cells, *bm* = basement membrane, *m* = muscle, *rc* = round cells, *g* = gland, *c* = cartilage Magnification, 70 diameters

Gastric content Ewald test meal Free acid, 8 per cent, combined acid, 37 per cent, total acidity, 45 per cent

Electrocardiogram Slight hyperbalance of right heart

Blood pressure 122/75

Medication—Potassium iodid, epinephrin and autogenous vaccine At the time of entrance to the hospital the patient suffered from two to four attacks of dyspnea daily, coughed a great deal, raised a small amount of sticky mucus and complained of pain in chest and of abdominal distention and distress

Ten minims of epinephrin usually gave prompt relief. However, after enjoying a period of quiescence for ten days, the patient died in an attack which had lasted three days. The necropsy was performed the next day.

NECROPSY REPORT *Anatomic Diagnosis*—Chronic fibrous myocarditis, marked emphysema of the lungs, barrel-shaped chest, hyperemia of the pericardial sac, passive hyperemia of the liver and spleen, slight chronic interstitial nephritis and hyperemia of the kidneys, fibrous episplenitis, calvities and canities.

*Macroscopic Examination*²⁰—The body is that of a white man about 55 years of age, weighing approximately 100 pounds. Rigor mortis is marked and posterior lividity is present. Muscular development is fair and the bones are of medium size. The chest wall is bulging and the abdomen flat. The subcutaneous fat in the midline of the trunk in front has a maximum thickness of 5 mm. The inguinal rings are closed. The liver extends two finger breadths below the costal margin. The diaphragm on the right side extends upward to the middle of the fourth rib, on the left to the fifth interspace. **Thorax** The pericardial sac is blue, caused by the engorgement of the vessels which supply it. There is only the normal amount of fluid present. The apex of the heart is made up of the right ventricle. The pulmonary artery and the right heart contain only fluid blood. The wall of the left ventricle at its thickest portion measures 2 cm, the right, 7 mm. It weighs 320 gm. The heart muscle is pale red and slightly fibrous. The lungs are huge and are free from adhesions. They are red and black in color and bulge out when the sternum is removed in the usual manner. The cut sections are spongy and some blood flows from their surfaces. **Liver** The liver is reddish brown and weighs 1,450 gm. Its capsule is smooth, except in places where it has been adherent to the diaphragm. There is a yellow scar on the right lobe 8 mm in its largest diameter, which when cut does not extend into the liver substance. The cut surfaces are red and exude much blood. **Kidneys** The kidneys together weigh 230 gm. Their capsules are smooth, but strip with difficulty, leaving a rough irregular surface. The cut surfaces are red and the cortical markings are fairly distinct. **Spleen** The spleen is rough and slaty blue, except the rough surface made up of yellowish nodules averaging 2 mm in diameter. The cut surfaces are very red and pulpy, much blood flowing from these surfaces. It weighs 150 gm.

Microscopic Examination—The pleura varies in thickness from 0.06 to 0.09 mm, and shows no abnormalities except a few widely distended blood vessels. The alveoli are not abnormally distended, except in patches in the periphery of the upper lobes of both lungs and they are empty, except in the left lower lobe where a few small areas are obliterated by accumulations of a fine granular precipitate which contains only a few erythrocytes. The alveolar walls throughout both lungs are thickened by distention of capillaries and an occasional accumulation of small mononuclear cells. The epithelium of the ductuli respiratorii is intact and shows no abnormalities. The walls of these passages contain short muscle bundles from 0.010 to 0.015 mm in thickness and only a few small mononuclear cells.

The bronchioles in all parts of the lungs are similar in structure. In a few of the smaller bronchioles the lumina are narrowed by a deep folding of the epithelium (Plate 2 A). In a few others the lumina are occluded by a fine granular precipitate containing only a few large pigmented mononuclear cells, while in the majority the lumina are patent and contain only a few of the pigmented cells. The epithelium is well preserved, is thrown into longitudinal folds varying in height from 0.010 to 0.085 mm and having a thickness in the smaller bronchioles of from 0.0075 to 0.020 mm and in the larger bronchioles from 0.050 to 0.095 mm. No goblet cells are visible. The basement membrane is not conspicuous. The subepithelial layer is thin and contains only a very few

20 Only those parts of the complete necropsy reports which seemed to have a possible relationship to the problem of our study are given here.

mononuclear cells The muscle layer, varying in thickness from thin strands to definite bundles 0.060 mm thick, does not form a continuous layer and varies greatly in size in different parts of the circumference of the bronchiole The elastic tissue is scanty and the fibrous tissue is found only in moderate amounts

The structure of the bronchi in all parts of the lungs is essentially the same The lumina of all contain only a small amount of granular precipitate in which there are fragments of desquamated epithelium The epithelium is thrown into longitudinal folds from 0.06 to 0.24 mm high and contains only a few goblet cells There is no evidence of new or old ulcer formation in the epithelium The basement membrane is visible only in parts of the circumference The subepithelial layer is thin and contains distended capillaries, scattered small mononuclear cells, a few polymorphonuclear eosinophil cells, plasma cells and small bundles of elastic tissue The muscle layer, which in many bronchi lies unusually near the epithelium, is very well developed, the bundles in some of the larger bronchi being 0.23 mm in thickness (Fig 4) These bundles, as seen best in the longitudinal sections, are separated from each other by only a thin connective tissue layer containing distended capillaries (Plate 1 D, and E) The mucous glands are of moderate size and their acini are small Most of the glands contain dense foci of small mononuclear cells, and in many of them only small fragments of gland tissue remain The outer portions of many of the glands contain many fat cells Many of the gland ducts in the subepithelial layer are surrounded by a wide zone of closely placed small mononuclear cells, and in many ducts the lumina form conspicuous ampullae-like enlargements between the cartilage and muscle layer These ampullae-like structures contain a small amount of mucus in which there is much desquamated epithelium The cartilages are unchanged The distended capillaries in all layers of the bronchi are very conspicuous and show well their distribution in these structures The walls of many of the bronchial arteries in the larger bronchi are very thick The ganglia, nerves and nerve sheaths are not infiltrated or surrounded by cells

Comment—The most significant pathologic changes in this case are (1) The numerous large gland duct ampullae (2) The extensive cellular infiltration in the bronchial mucous glands (3) Small size of bronchial mucous glands and abundant periglandular collections of fat cells (4) Prominence of the bronchial muscular system (5) Thickening of the walls of the bronchial arteries The history of a severe bronchitis preceding and accompanying the attacks of dyspnea, of asthmatic attacks beginning about the fiftieth year and the microscopic evidence of infection of the bronchial mucous glands point to bacteria as the causal agents in this case of asthma

CASE 3—Miss L, aged 17, entered the Cook County Hospital suffering from an acute infection

History—Since early childhood she had had frequent severe attacks of spasmodic dyspnea which were always worse in summer and were accompanied by severe coughing and raising of a thick sticky sputum The attacks, while less frequent in the past year, had become more severe in character

Family History—Negative

Examination—Pulse, 116, respiration, 28, temperature 99.4 F, blood pressure, 110/72 Blood Hemoglobin, 75 per cent, leukocytes, 17,200, red blood cells 4,420,000 Differential count small lymphocytes, 8 per cent, large lymphocytes, 2 per cent, neutrophils, 84 per cent, eosinophils, 5 per cent,

transitionals, 1 per cent Marked pyorrhea alveolaris, bilateral cervical adenopathy

Urine Positive for albumen and casts Thorax increased anteroposterior diameter, normal lung borders, diminished excursion on both sides, percussion note hyperresonant over whole chest, numerous wheezing and squeaking râles on both sides, one small area of crackling râles over the medium dependent portion of the left lower lobe Heart Heart tones indistinctly heard, no murmurs Abdomen Negative Adenopathy of axillary and inguinal glands Reflexes, normal

Diagnosis—Bronchial asthma, localized patch of bronchitis, emphysema, nephritis and pyorrhea alveolaris

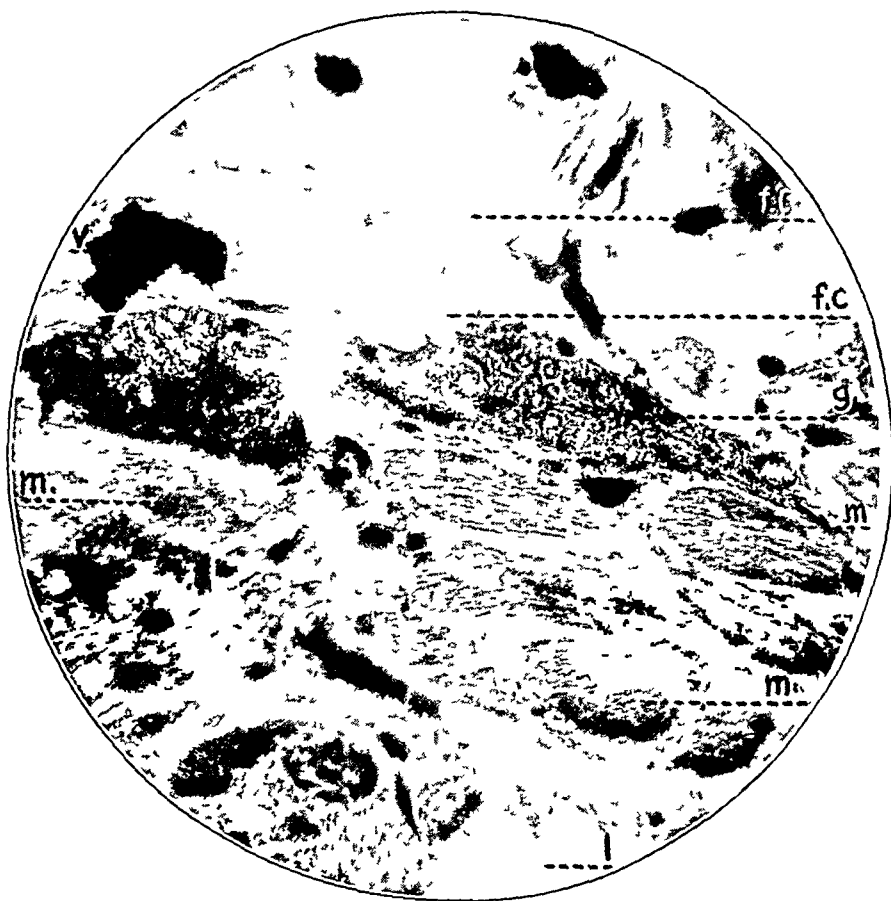


Fig 4—Case 2 Bacterial asthma Large bronchus Cross section Epithelium desquamated Basement membrane not visible Subepithelial layer contains few cells Muscle bundles large Glands small and contain foci of round cells All vessels distended *l*=lumen, *m*=muscle, *g*=gland, *fc*=fat cells, *v*=vein Magnification, 45 diameters

Course—There was a steady improvement in condition for sixteen days, then a sore throat developed, with abdominal pain, vomiting and other symptoms of acute intoxication The patient died three days later

NECROPSY REPORT (Dr Stangl) *Anatomic Diagnosis*—Acute hemolytic streptococcus pericarditis and peritonitis, cloudy swelling of myocardium, liver and kidneys, acute emaciation, fibrous obliteration of the right pleural cavity, hyperplasia of the spleen Bacterial cultures of pericardial fluid and heart blood showed hemolytic streptococci

Macroscopic Examination—The body is that of a small, poorly nourished white girl about 12 years of age. Height 146 cm. The lips and fingers are cyanotic. The thyroid is slightly enlarged. The skeletal muscles are well developed. The axillary lymph glands are somewhat enlarged. Abdomen. The abdominal cavity contains a large quantity of a brownish fluid in which are flocculi of fibrin. The omentum hangs low and is covered with fibrin. The peritoneal surface of the intestines is reddened and coated with fibrin. The lower border of the liver is at the costal margin. There are fibrous adhesions between the fundus of the gallbladder and the stomach and duodenum. The diaphragm reaches to the fifth rib on the right side and to the fourth rib on the left. Pleural cavity. The right pleural cavity is entirely obliterated by fibrous adhesions. The left cavity is free of adhesions. There

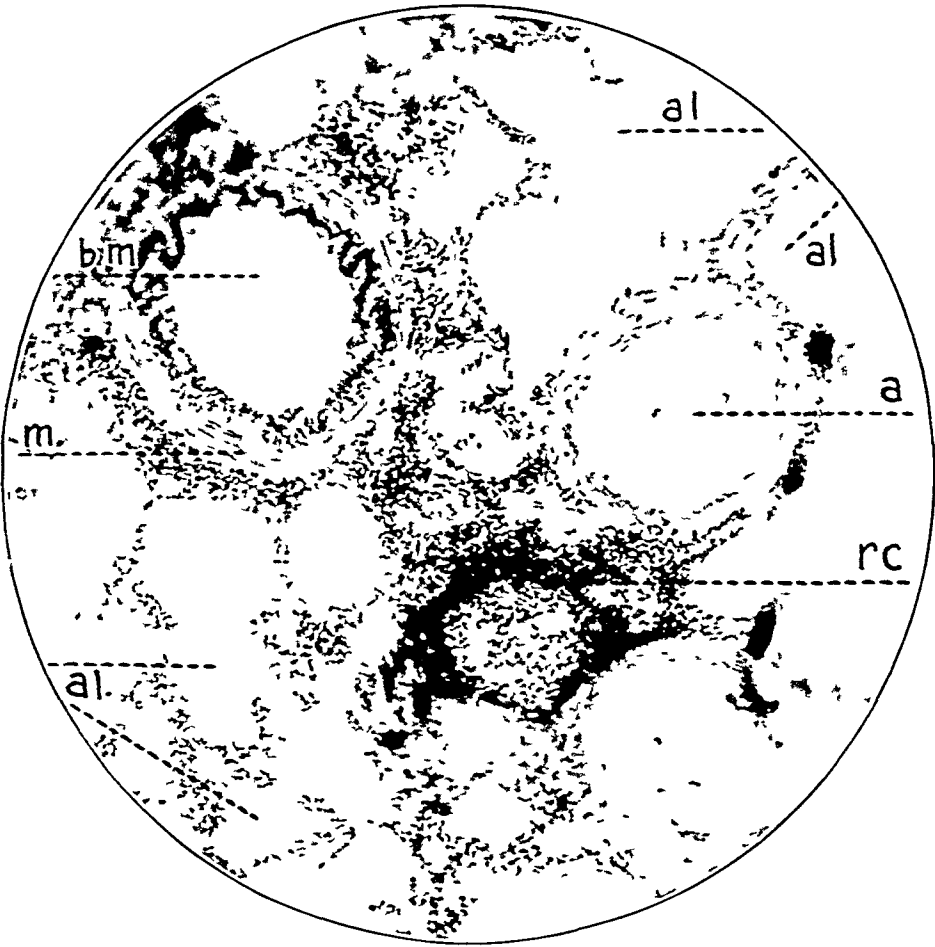


Fig 5—Case 3 Food (?) asthma. Bronchiole. Cross section. Muscle layer prominent. Area of round cells. *br*=bronchiole, *m*=muscle, *a*=artery, *al*=alveoli, *rc*=round cells. Magnification, 85 diameters.

is a moderate amount of granulation tissue at the site of the thymus. Pericardial cavity. The pericardial cavity contains a small amount of turbid fluid in which there is fibrin. There are many petechial hemorrhages beneath the epicardium. Heart. The venae cavae are engorged with dark clotted blood. The tricuspid and aortic valves are normal. There is a healed vegetative growth on one cusp of the mitral valve. The myocardium is pale red and grossly without change. The heart weighs 400 gm. Lungs. The surface of the right lung is covered by extensive fibrous adhesions, but it crepitates everywhere and is free from coal dust pigmentation. It weighs 320 gm. The surface of the left lung is smooth and it crepitates everywhere. The trachea and

bronchi exude a thick mucopus and the mucosa is hyperemic. The tracheo-bronchial lymph glands are brown in color. Liver The liver is mottled reddish brown and yellow and its capsule is smooth and dull. Spleen Large and firm and weighs 320 gm. The solitary lymph follicles of the large intestine are prominent (2 mm), and some are surrounded by small hemorrhages. There is one small cyst in each ovary. Kidneys Weight, 400 gm, mottled in color, fetal lobulations. The capsule is smooth and strips readily, leaving a smooth surface. The cortical striations are plainly visible. The lining of the pelvis is smooth and unchanged. Head The brain and meninges show no gross changes.

Microscopic Examination—Left lung examined. The pleura is slightly thickened throughout and contains numerous small foci of small round cells. Most of the alveoli are small, containing only a few pigmented endothelial cells, and their walls are considerably thickened by dilated capillaries, and numerous small accumulations of small round cells. The remaining alveoli are moderately dilated, contain no exudate and have thinner walls.

The bronchioles in the whole lung vary markedly in size and structure, some being dilated and with thin walls, others being markedly contracted. In some the folds of epithelium have sloughed off and completely occluded the lumen (Plate 2 B). The lumina of the former vary in size from 0.25 to 0.5 mm and the latter from 0.07 to 0.15 mm. The other measurements are given in Table 1. The single layered low cuboidal epithelium is intact and the subepithelial layer contains a few small round cells, a small amount of elastic tissue and an occasional polynuclear eosinophil cell. The muscular layer in some bronchioles form a distinct complete circular ring but in most it is interrupted (Fig 5).

The lumina of the smaller and medium sized bronchi contain only a small amount of exudate which adheres to the epithelium and consists chiefly of mucus containing epithelial cells either isolated or in clumps. Among these cells there are a few polymorphonuclear neutrophils and eosinophils and a few round cells. The epithelium is intact except in the deeper cryptlike pockets between folds where only the lower layer of cells remains. The outer layer of the epithelium contains numerous goblet cells and in some bronchi there are a few small round cells and polynuclear eosinophil cells between the epithelial cells. There is no appreciable lengthening of the epithelial cells in any portions of the bronchi. The basement membrane is distinct and appears normal even in the bronchioles.

The subepithelial layer varies considerably in thickness even in the same bronchus, as is well shown by the longitudinal sections. This layer, especially that portion lying nearest the basement membrane, is infiltrated by numerous small round cells, plasma cells and a few polymorphonuclear eosinophil cells. The longitudinal and circular bundles of elastic tissue are not increased in size and the capillaries are not distended.

The muscular layer in all bronchi is well developed and shows especially in the longitudinal sections the distinct bundle arrangement (Fig 6). The connective tissue separating and extending into these bundles contains a few polymorphonuclear eosinophil cells and a few small round cells.

The mucous glands which are found in all bronchi having an outside diameter greater than 2 mm are large and most are infiltrated extensively by small round cells. The acini of the glands are not in active secretion and in many glands they are distorted and widely separated by the infiltrating round cells, while in some glands only a few small acini remain. The walls of the mucous-gland ducts contain many round cells and the tissue around many and form distinct ampullae containing mucus, desquamated epithelium and round cells. No eosinophil cells are found in any of the glands.

Cartilages are found in smaller divisions of the bronchi than the glands and many contain small calcified areas. One cartilage in a small bronchus with an outside diameter of 2.8 mm contains a small ossified portion with a true marrow center (Fig 7).

The walls of the bronchial arteries are moderately thickened and the nerves and ganglia are surrounded by connective tissue containing only a few round cells.

The content and walls of the larger bronchi are similar to that in the smaller bronchi, except that the goblet cells are somewhat more numerous in the former. There is no essential difference in findings in the bronchi of the upper and the lower lobes. Measurements of the bronchi will be found in Table 2.

Comment—The most significant pulmonary pathologic findings in this case are (1) Right sided adhesive pleuritis (2) Extensive

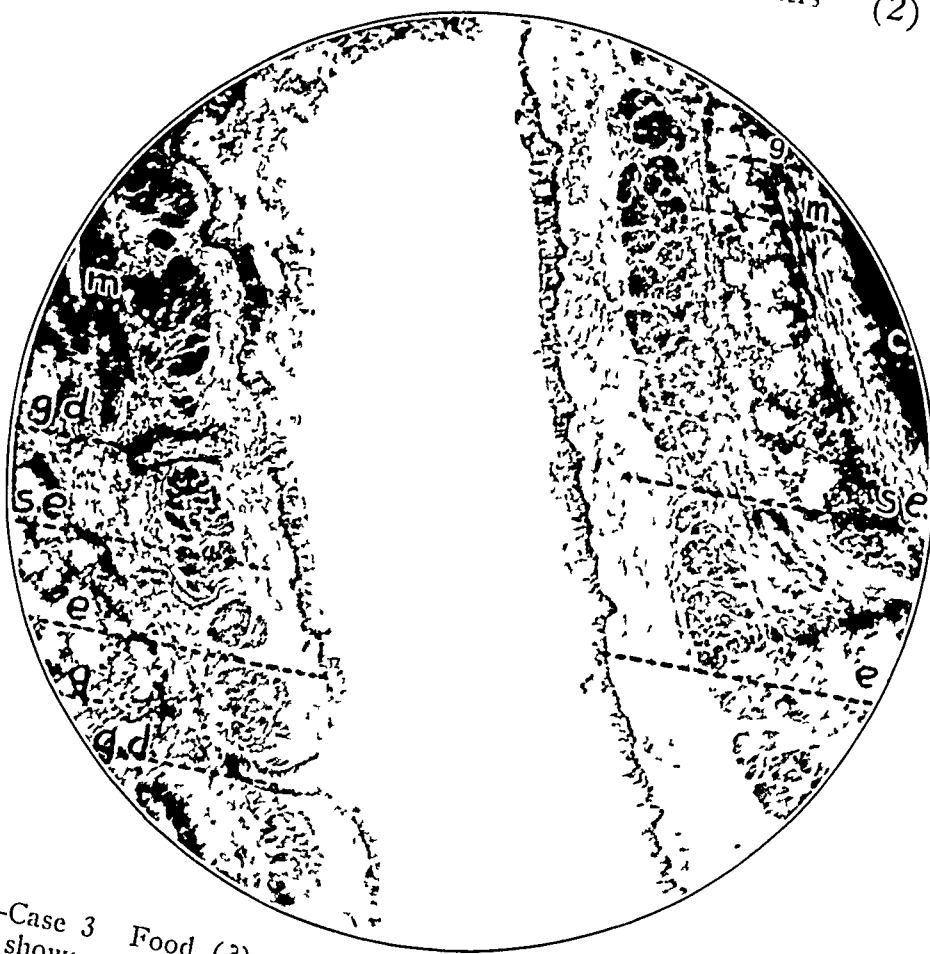


Fig 6—Case 3 Food (?) asthma Small bronchus Longitudinal section Epithelium shows goblet cells Basement membrane prominent Subepithelial layer infiltrated by round cells Muscle bundles prominent Glands contain round cells *c*=epithelium, *gc*=goblet cells, *se*=subepithelial layer, *m*=muscle, *gd*=gland duct, *g*=gland, *c*=cartilage Magnification, 45 diameters

(4) Prominence of muscle layer (5) Calcification and ossification of walls of mucous-gland ducts (3) Numerous ampullae-like gland ducts cellular infiltration of the subepithelial layer, the mucous glands, and the walls of mucous-gland ducts (6) Eosinophilic infiltration of bronchial wall cartilages

The history of asthma since childhood suggests the probability of sensitization to plant or animal proteins This point cannot be determined definitely, as no skin sensitization tests were made and a complete clinical

history was not obtainable. The evidence of an old infection, the adhesive pleuritis, and the evidence of present infection in the mucous glands and the subepithelial layer of the bronchi point to bacteria as secondary agents in this case of asthma.

CASE 4—Mr. E. L., aged 29

History—The complete history is not available. Patient had had frequent head colds and asthmatic attacks since the age of 10 and was unable to do any work until his twenty-seventh year when, following medication and use of an autogenous vaccine there was a period of improvement.

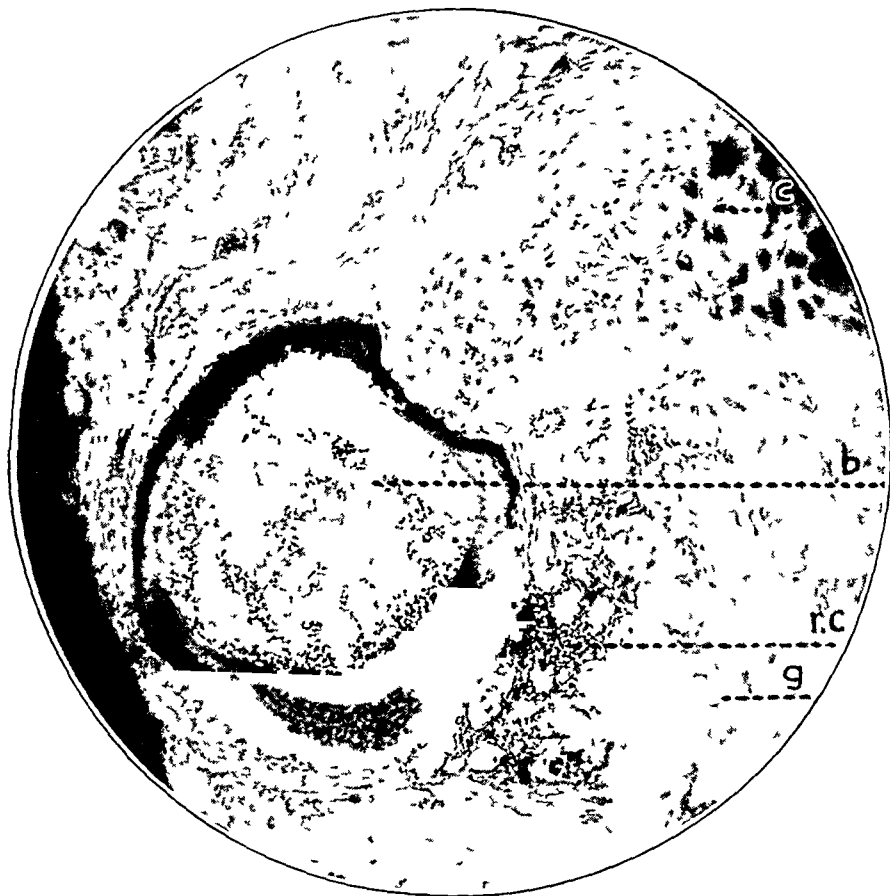


Fig. 7—Case 3. Food (?) asthma. Bronchial cartilage with ossification. *b* = bone with typical bone marrow, *rc* = round cells, *g* = gland, *c* = cartilage. Magnification, 70 diameters.

Family History—Mother had asthma after thirty-fifth year.

Course—While in the army he discovered that proximity to horses or mules precipitated attacks of asthma and he therefore wished to be desensitized. This was attempted by his physician and death occurred within ten minutes after an intravenous injection of 1 minim of horse serum. Here we need give only a few points of particular interest, as the complete report of the necropsy findings is given by Boughton.¹ He says in part

¹ 21 Boughton, T. H. Anaphylactic Death in Asthmatics, J. A. M. A. 73: 1912 (Dec. 29) 1919.

Both lungs were enormously distended and emphysematous. The left lung showed a small area of hemorrhage on the lateral portion of the lower lobe, about 4 cm in diameter, with a gelatinous organizing exudate at this point. On section the lungs are dry. The right pleural cavity was largely obliterated by firm fibrous adhesions. No fluid was present in either cavity. The heart was firm and of normal size and appearance except for a few subpericardial petechial hemorrhages on the posterior surface.

Microscopic Examination—Lungs. There was a moderate passive hyperemia, but no edema. There were a few small interstitial hemorrhages. A little mucus and a few desquamated epithelial cells were seen in some of the bronchioles. The peribronchiolar muscle was well developed. A few arteries showed greatly thickened walls, and many showed a moderate thickening of the walls. Eosinophils were very numerous in the spleen.

Microscopic Examination—Drs. Boughton and Raulston, the pathologists, kindly furnished us with the blocks of tissue from this case so that we could make a more detailed study of the lungs. Our findings are as follows. The structure of the pleura varies from a thin layer 0.09 mm thick with no appreciable changes to a layer 1.35 mm thick. This increased thickness is due chiefly to fibrous tissue, the outer layer of which is less compact and contains numerous small extravasations of erythrocytes. The pleura, especially in the thickened portion, contains numerous small capillaries, scattered small round cells, a few small foci of round cells, but no eosinophil cells. In some obliterated interlobar spaces and in portions of thickened pleura, where adhesions are evident, small thick-walled arteries are very conspicuous. The alveoli have no uniformity in size due to the unusual variation in structure of the interstitial tissue. Some are widely dilated and have thin intact or ruptured walls while those adjoining may be small and have walls thickened by fibrous tissue and cellular infiltration. The lumina of most of the alveoli contain only an occasional large pigmented mononuclear cell, but in a few small areas they are completely filled by a finely granular precipitate containing an occasional erythrocyte. The patchy thickening of the interstitial tissue is very striking and in many parts of the lungs patches of alveoli are almost completely obliterated by a dense tissue which consists of a network of fibrous tissue surrounding various sized groups of cells. These cells are chiefly small round cells, often grouped, with densely stained nuclei and scanty cytoplasm, large cells with small nuclei and abundant homogeneous cytoplasm, plasma cells, pigmented endothelial cells, a few polymorphonuclear neutrophil cells and an occasional polymorphonuclear eosinophil cell. Throughout this tissue there are numerous fragments of hyperplastic epithelium, some small isolated bronchioles with walls that are densely infiltrated by small round cells, and which are surrounded by a thick zone of fibrous tissue, thin strands of non-striated muscle fibers, and numerous small thick walled arteries surrounded by a thick zone of dense fibrous tissue.

The epithelium of the ductuli respiratorii is intact and the supporting layer of tissue contains numerous small round cells, a few polymorphonuclear eosinophil cells, and in many places short bundles of smooth muscle from 0.01 to 0.02 mm thick.

The smallest bronchioles contain only an occasional pigmented mononuclear cell and their lumina are narrowed by longitudinal folds of epithelium from 0.03 to 0.04 mm high. The epithelium is intact and contains no goblet-like cells. The basement membrane appears hyaline and is distinctly visible for only parts of the circumference. The subepithelial layer contains numerous small mononuclear cells, a few polymorphonuclear eosinophil cells, a few plasma cells, and a few constricted capillaries (epinephrin effect?). The muscular layer varies greatly in thickness in different bronchioles and does not form a continuous band. The outer layer of tissue is composed of loose fibrous tissue in which are many cells similar to those in the subepithelial layer.

The larger bronchioles are almost filled by a granular precipitate which contains only a few cells, chiefly pigmented mononuclear cells, a few neutrophil polymorphonuclears, and a few erythrocytes. The epithelium is from 0.027 to 0.05 mm high and forms longitudinal folds from 0.12 to 0.18 mm high. The portion of the epithelium nearest the lumen is made up of long ciliated

cells among which are numerous goblet-like cells. The deeper portions of the epithelium contain numerous small round cells. The other layers of the wall are similar to those of the smaller bronchioles except that the muscle layer forms larger bundles and the cellular infiltration is more marked. In the outer portion of the walls of many of these bronchioles there are masses of fibrous tissue from 0.21 to 0.50 mm in thickness surrounding arteries with irregularly thickened walls. These vessels suggest the nodal arrangement of the bronchial arteries of guinea-pigs that have succumbed to anaphylactic shock² (Figs 8, 9 and 10).

The lumina of the small bronchi contain only a small amount of a granular precipitate similar to that in the larger bronchioles. The epithelium, which is similar in structure to that in the larger bronchioles, is from 0.09 to

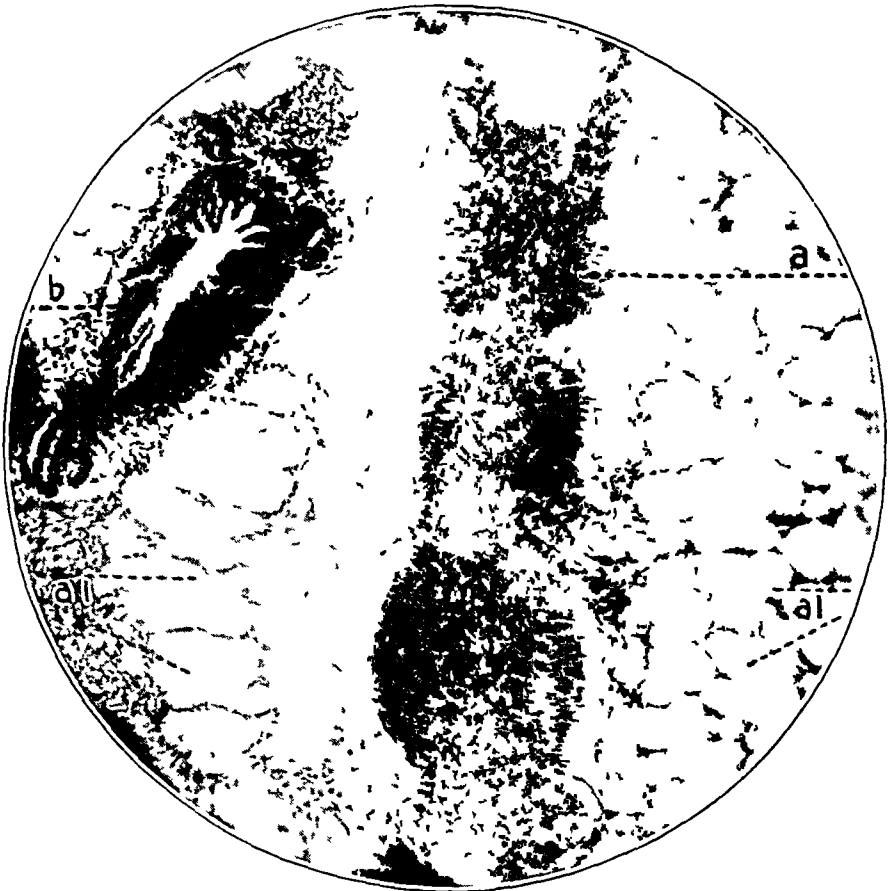


Fig 8—Guinea-pig Fatal horse serum anaphylaxis. Artery. Nodular thickening of muscle. *a*=artery, *al*=alveoli, *b*=bronchiole. Magnification 90 diameters.

0.12 mm high and is thrown into folds from 0.20 to 0.27 mm high. The basement membrane is thick and hyalin in appearance. The subepithelial and muscular layers are similar to those in the bronchioles but are markedly thicker. The mucous glands are almost completely obliterated by infiltration of small mononuclear cells, only a few atrophic acini remaining in most of the glands. The gland ducts are small and their walls are infiltrated by many

²² Schultz, W. H., and Jordan, H. E. A Microscopic Study of the Anaphylactic Lung of the Guinea-Pig and Mouse, *J. Pharmacol. & Exper. Therap.* 2: 375, 1911.

small mononuclear cells Throughout the tissues studied there is no evidence of new ulcer formation in the epithelium and no evidence of healed ulcers except possibly localized collections of small round cells in the subepithelial layers (Fig 11)

The pulmonary and bronchial arteries and veins in many parts of the lungs are surrounded by varying amounts of dense fibrous tissue containing a few round cells and ranging in thickness from 0.15 to 0.5 mm The media of many bronchial arteries is irregularly thickened and measures 0.18 mm in some cases with a diameter of 0.45 mm The walls of many smaller arteries contain areas of calcification The spleen contains a large number of polymorphonuclear eosinophil cells

The cartilages show some areas of calcification and one cartilage contains a small calcified area surrounding typical bone marrow

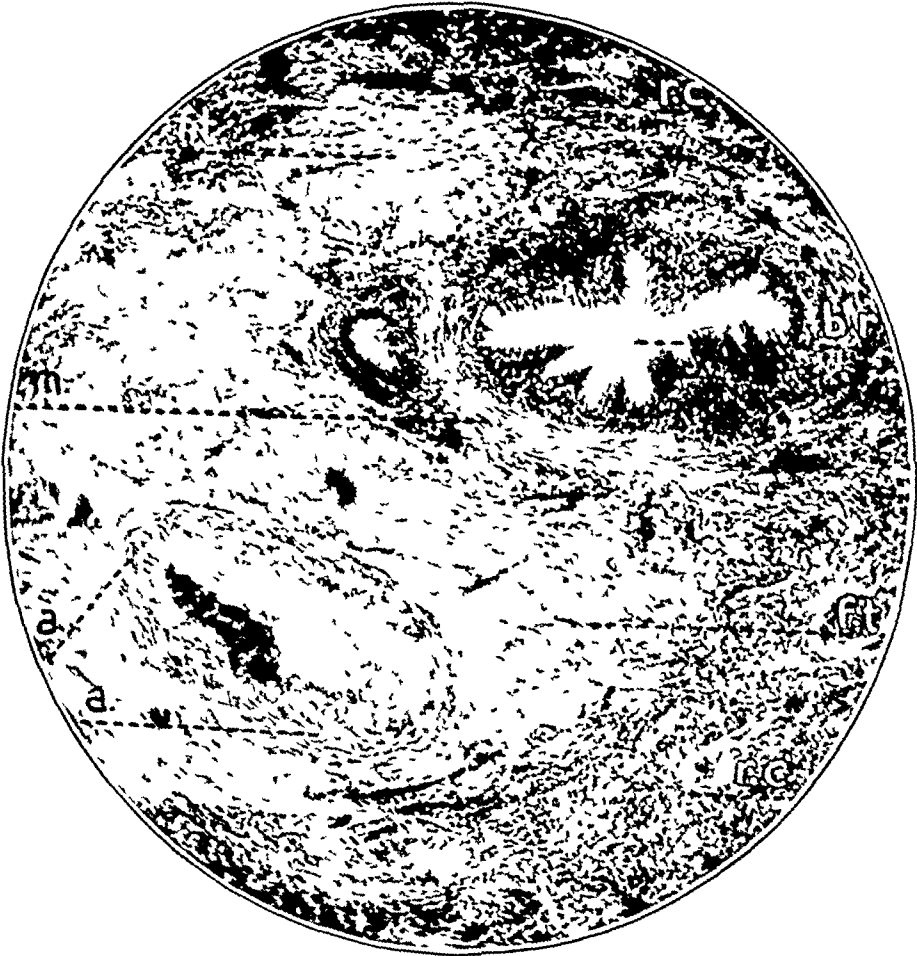


Fig 9—Case 4 Horse asthma Fatal horse serum anaphylaxis Artery and bronchiole surrounded by fibrous tissue *a* = artery, *b* = bronchiole, *m* = muscle, *ft* = fibrous tissue Magnification, 60 diameters

Comment—The most significant pathologic findings in this case are (1) Right sided adhesive pleuritis (2) Completely consolidated areas of pulmonary tissue (3) marked cellular infiltration of the walls of the bronchi and bronchioles (4) Moderate thickening of muscle tissue in the bronchi (5) Atrophy of bronchial mucous glands (6) Thickening of the walls of many pulmonary and bronchial arteries (7) Wide zone of fibrous tissue surrounding many pulmonary and bronchial

arteries (8) Eosinophilic infiltration in bronchial wall and in the spleen (9) Calcification and ossification of bronchial cartilages

The history of head colds and asthma since the tenth year with the subsequent discovery of the sensitiveness to horse dander leads one to believe that this case was from the beginning one of horse asthma. The adhesive pleuritis, the areas of consolidated lung tissue, and the evidence of extensive bronchial infection cannot be overlooked and the question naturally arises whether these factors are the result of the asthmatic attacks or are implicated in the production of the attacks.

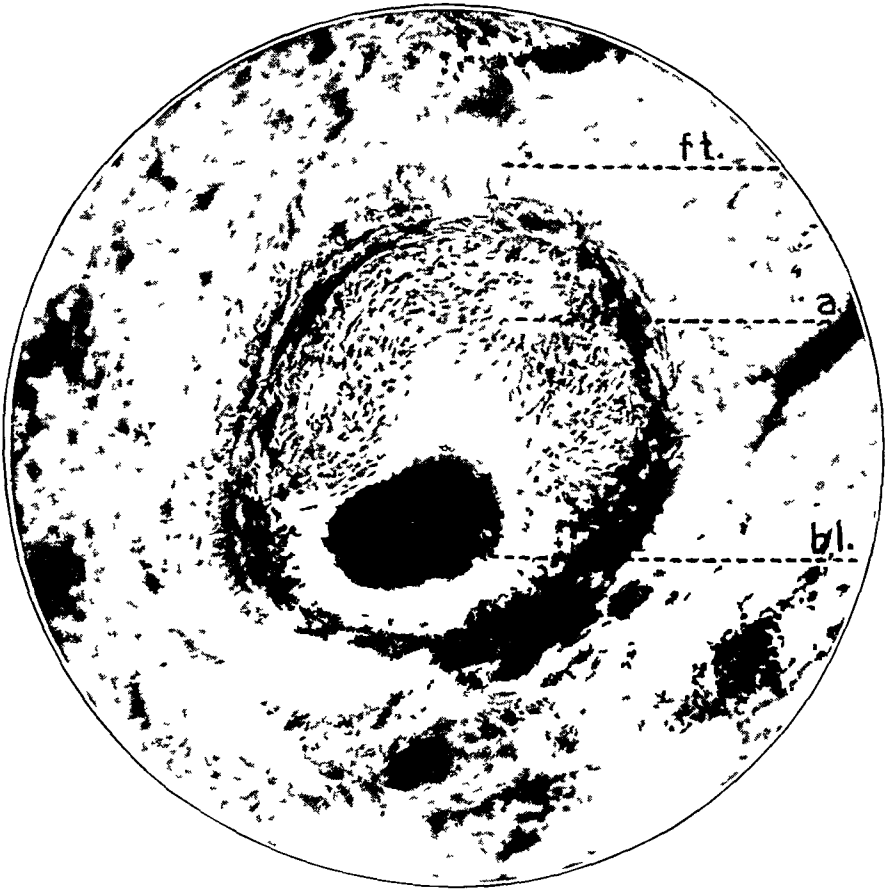


Fig 10—Case 4 Horse asthma Fatal horse serum anaphylaxis Artery surrounded by fibrous tissue and having irregularly thickened walls *a*=artery, *bl*=blood, *ft*=fibrous tissue Magnification, 100 diameters

CASE 5—Mr L, aged 32, single, American, car repairer

History—Previous illnesses Measles, whooping cough and malaria From childhood until going to California in his twenty-fourth year he suffered from frequent paroxysmal attacks of dyspnea After a free period of seven years in California he returned to Chicago six months before death and suffered from a recurrence of the attacks One week before death, April 4, 1912, he entered the Cook County Hospital suffering from bronchopneumonia

Physical Examination—Slightly built white male Head and eyes negative Chest Supraclavicular fossae deep, epigastric angle wide, accessory respira-

tory muscles used during respiration, coarse sibilant râles heard posteriorly Heart and abdomen negative Urine contains erythrocytes Sputum, no tubercle bacilli Blood differential count Neutrophils, 84 per cent, large mononuclears, 8 per cent, small mononuclears, 8 per cent Temperature, 102 F The condition of the patient gradually became worse and death occurred seven days after entrance Postmortem examination by Dr H G Wells

NECROPSY REPORT *Anatomic Diagnosis*—Acute, left, serofibrinous pleuritis, abscess in the lower lobe of the left lung, pulmonary emphysema, fibrinous pneumonia of the posterior portion of the left upper lobe, bronchopneumonia in right lung, chronic bronchitis, acute mediastinal lymphadenitis, slight hypertrophy of the right ventricle

Macroscopic Examination—External appearance The body is that of a poorly nourished man, height 160 cm The chest is very prominent antero-posteriorly, the costal cartilages bulge forward, particularly on the right side, and the intercostal spaces are considerably increased in width The diaphragm reaches to the fifth interspace on the right side, to the sixth rib on the left side Thorax The right pleural cavity contains no fluid The left cavity, however, contains considerable fluid which is turbid, blood stained, and full of fibrin The serous membrane of the pericardium is smooth and shining, and shows no evidences of inflammation Mouth The pharynx is normal except for a slight edema about the arytenoids Heart Contracted and extremely rigid Its size and proportions are apparently normal except for a slight hypertrophy of the right ventricle Its weight is about 300 gm The walls of the right ventricle are very muscular, averaging 4 mm in thickness The aortic, pulmonic, mitral and tricuspid valves all appear normal Neither the aortic ring nor the thoracic aorta show any sclerosis Lungs The right lung is adherent anteriorly to the chest wall by weak fibrous adhesions, while its base is attached by firmer adhesions to the diaphragm The lung itself shows no tendency to collapse and on being placed in water floats high The substance of the lung itself is soft, pale, spongy and inelastic Palpation reveals slight nodular and irregular hardenings The pleura shows evidences of hemorrhage The cut surface appears slightly raised, and mottled with the irregular hardened areas of bronchial pneumonia Posteriorly this lung is full of fluid The left lung, externally, appears light in color much as if it had been boiled Like the right lung it does not collapse The lower lobe is small, due to the compression of the fluid found in the left pleural cavity, and its lower portion contains much fluid Its cut surface reveals prominent, thickened bronchi, and in one place a small abscess, 5 x 8 mm, which lies just beneath the pleura Over this abscess the fibrin is much thicker and whiter than elsewhere The upper lobe presents in its posterior portion a diffuse consolidation such as is seen in very wet, early pneumonia, such as is secondary to edema The walls of the bronchi in this lobe are also thickened There are no evidences of tuberculosis

Peribronchial lymph glands Are enlarged and reddened due to their proximity to the adjacent pleuritis None caseous or calcified Liver Weight, 1,400 gm The cut surface shows the lobules to be well marked and slightly darker at their periphery Spleen The spleen is of normal size, pinkish gray and soft Gastro intestinal tract In the lower portion of the ileum Peyer's patches show some slight pigmentation such as frequently follows typhoid

Microscopic Examination—Spleen The malpighian corpuscles are small, increase in number of trabeculae, hyaline changes around the arteries Liver Shows slight passive hyperemia Heart muscle Slight increase in connective tissue Lungs There is an increase in the connective tissue around the arteries and bronchi The alveolae are filled with desquamated cells and fibrin and some polymorphonuclears Some of the alveolae show edema Some areas show beginning abscesses The mucous glands show hyperplasia Kid-

ney There is fibrosis of some of the glomeruli with round cell infiltration under the capsule There are some albuminous casts in the tubules Lymph glands The glands show a great deal of anthracosis, some hyperplasia and some eosinophils

Detailed Histologic Examination—A systematic study of the lungs of this case was not possible as only portions of the lungs were preserved Our findings are as follows The pleura, with a fairly uniform thickness of from 0.075 to 0.15 mm contains numerous distended capillaries, scattered small round cells, and a few small foci of round cells The lung structure are obliterated in patches by pneumonic foci which are surrounded by alveoli containing a granular precipitate and in some areas extravasations of erythro-

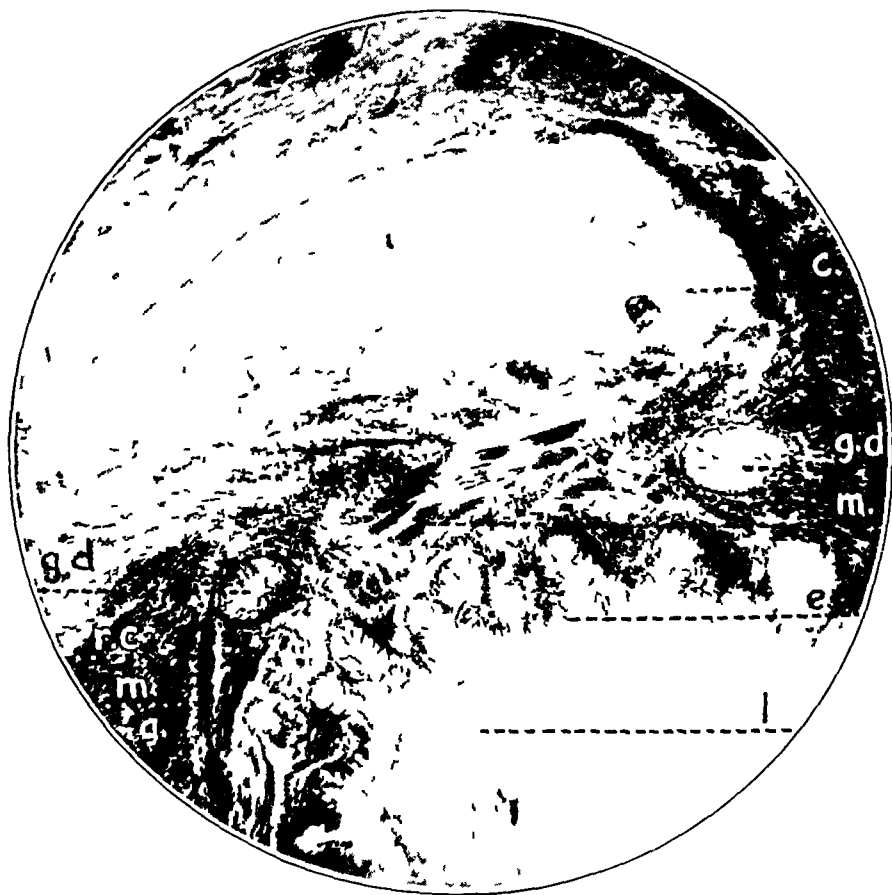


Fig 11—Case 4 Fatal horse serum anaphylaxis Small bronchus Cross section Epithelium swollen Subepithelial layer infiltrated by round cells Glands small and infiltrated by round cells *l*=lumen, *e*=epithelium, *m*=muscle, *g*=gland, *g d*=gland duct, *c*=cartilage Magnification, 45 diameters

cytes The alveolar walls in the areas not involved in the pneumonic process are not appreciably changed

The lumina of the smaller bronchioles are partially occluded by fragments of desquamated epithelium, polymorphonuclear neutrophil cells, and a few erythrocytes The single layered epithelium is partially desquamated and the basement membrane is indistinct The subepithelial layer contains numerous small mononuclear cells, a few plasma cells, a few polymorphonuclear neutrophil cells and some distended capillaries The muscle bundles are small and do not form a continuous layer The larger bronchioles are similar to the

smaller, except that all layers are proportionately better developed. The elastic and fibrous tissues are very scanty in all the bronchioles.

The lumina of the small middle-sized bronchi contain the same character of material as that found in the bronchioles. The stratified epithelium is almost completely desquamated and the basement membrane is inconspicuous. The subepithelial layer is markedly thickened and contains many small mononuclear cells, a few polymorphonuclear neutrophil cells, occasional polymorphonuclear eosinophil cells, numerous distended capillaries and small bundles of elastic tissue. The smooth muscle layer is not prominent and its short bundles are separated and more or less obscured by fibrous tissue and invading small mononuclear cells. The cartilages show only a few small calcified areas.

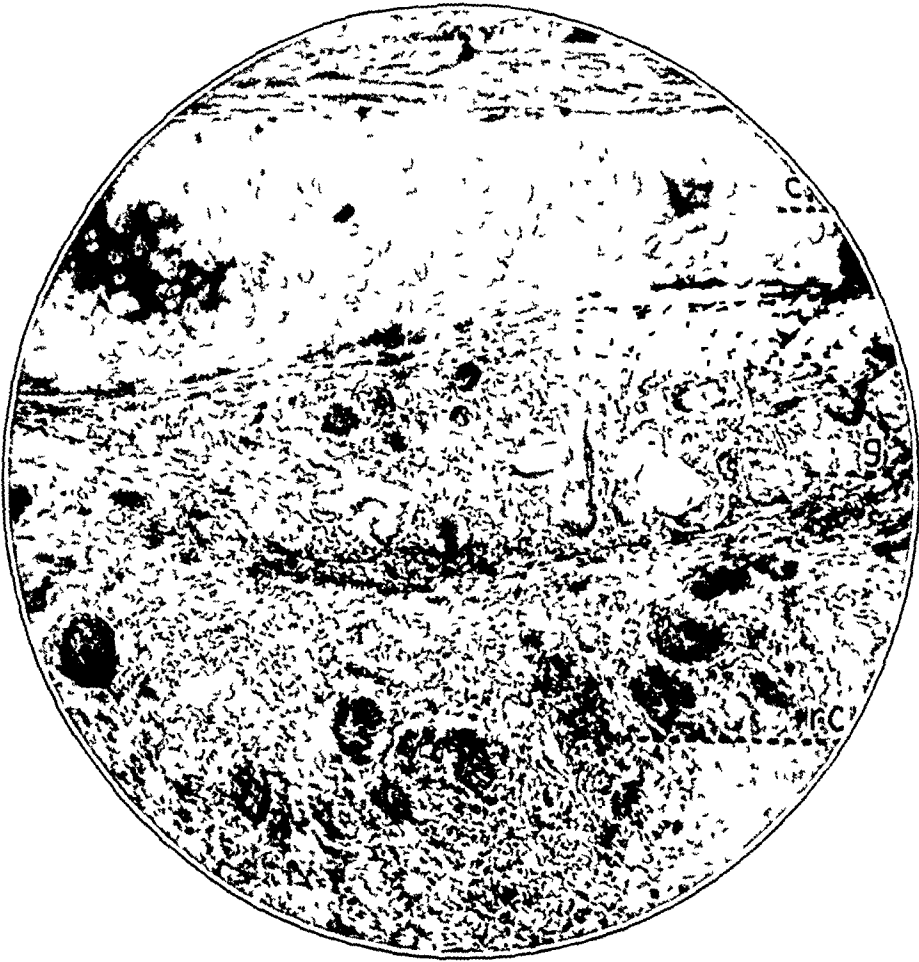


Fig 12—Case 5 Asthma Bronchus Cross section Subepithelial layer markedly infiltrated by round cells. Mucous gland infiltrated and containing hyperplastic acinar cells. *c* = round cells, *g* = gland, *c* = cartilage. Magnification, 60 diameters.

Most of the mucous glands are small then acini are few in number, markedly distorted and separated by a cell rich tissue containing plasma cells, small mononuclear cells, a few polymorphonuclear neutrophil cells, a few mononuclear eosinophil cells, and a type of cell with a large pale nucleus and an abundant homogenous cytoplasm. These acini may form small compact circular or tubular masses of cells, or they may form larger leaf shaped masses surrounding varying amounts of mucus. The acinar cells in these masses are larger than normal and contain large pale nuclei. In all the wall layers between the gland and the lumen there are many compact collections of a similar type.

of cell, the shape and distribution of which indicate that these masses are remnants of gland ducts (Fig 12)

The bronchial arteries have thickened walls involving chiefly the media and are not surrounded by increased fibrous tissue

The nerves are not appreciably changed and are not surrounded by small round cells

Comment—The most significant pathologic findings are (1) Partial occlusion of the lumina of bronchi and bronchioles by exudate (2) Infiltration of the subepithelial layer of bronchi and bronchioles by small round cells and eosinophil cells (3) Infiltration of mucous glands by small round cells (4) Hyperplastic changes in acinar cells of bronchial mucous glands (5) Slight hypertrophy of the right heart

The etiology of the asthmatic attacks in this case is not clear The history of attacks since early childhood with a free period following a change of climate and then a recurrence, could be interpreted either as sensitiveness to food or animal proteins or to infection in the respiratory tract

CASE 6—History—Infant M, female, aged 15 months Normal delivery Birth weight $8\frac{1}{2}$ pounds Family history is negative Breast fed for three months with a gain in weight to 15 pounds, but because of a facial eczema she was put on artificial feedings by the family physician At the eighth month she was admitted to the Children's Memorial Hospital Dispensary with eczema and weighing 11 pounds Under dispensary management the skin condition improved and the weight increased At the age of 12 months she was brought into the Children's Memorial Hospital suffering from a pharyngitis, accompanied by dyspnea and cyanosis of the face

First Examination—Well nourished Temperature 101.6 F, pulse, 160 Head negative except for reddening of both ear drums, cyanosis of the lips and facial eczema Neck, marked cervical adenopathy Thorax barrel shaped, markedly emphysematous and hyperresonant, marked expiratory stridor, squeaky râles all over the chest Abdomen distended and slightly tympanitic Genitalia and extremities negative Small doses of epinephrin and atropin gave only slight relief The dyspnea and stridor gradually subsided, but the eczema persisted Pus was obtained from both ears after paracentesis Urticarial lesions appeared on the abdomen, back, groin and face one-half hour after a feeding of farina, and subsequent cutaneous protein sensitization tests revealed a marked degree of sensitiveness to wheat proteins and to whole wheat and a slight degree of sensitiveness to cow's milk and to lactalbumin The reactions to orange egg yolk, egg albumin, beef, mutton, navy bean, spinach, carrot, cocoa, coffee, rye, oats and barley were negative Wheat protein and whole wheat, both of which gave definite reactions, were eliminated from the diet and oatmeal substituted as the cereal

Course—At the end of one week, the patient was discharged from the hospital with very little bronchitis, no râles in the chest, and much less of the facial skin involvement Six days later she was again admitted to the hospital suffering from an asthmatic attack which may have been brought on by the ingestion of wheat containing food Four days later the patient was again discharged from the hospital with very little bronchitis, no râles in the chest and no eczema For two months her condition improved, wheat containing foods having been gradually added to the diet, then she was again admitted to the hospital suffering from a cold in the head and an attack of asthma

Second Examination—Leukocytes, 7,950 Hemoglobin (Sahli), 96 per cent Respiration 64 A fairly well-developed and nourished female child with

respiratory difficulty and markedly cyanotic. She has a marked respiratory wheeze and the accessory respiratory muscles are used. The head is inclined to be square shaped and is held in a retracted position. The anterior fontanel is open and bulging and quite tense. Craniotabes is present. Skin of the cheeks is rough. Chest is inclined to be barrel shaped, and on percussion there is a hyperresonant note over the entire chest. The heart tones are hard to hear on account of the wheezing noises in the chest. The liver is two fingers' breadth below the costal margin in the mammary line. The spleen is not palpable. There are no tumor masses in the abdomen. The knee reflexes are active. The use of epinephrin, atropin and benzyl benzoate afforded only transient relief and the patient died about thirty-two hours after entering the hospital. The postmortem examination was made a few hours later by Dr W G Hibbs.

NECROPSY REPORT (Only the most important findings are given)

Anatomic Diagnosis—Huge hypertrophic emphysema of the lungs. "Barrel-shaped" chest. Downward displaced diaphragm and liver. Hypertrophy of the right ventricle of the heart. Slight passive hyperemia of the liver, kidneys and skin. Hypertrophy of the thymus, cervical and mesenteric lymph nodes, the spleen, the lymphoid tissue of the base of the tongue and the lymph nodes of the ileum. Narrowed aorta (congenital). Fatty changes of the liver. Needle puncture wounds of the upper arms. Suppurative vaginitis (gonococcus). Hyperemia of the uterus and adnexa. Eczema (?) of the skin of the face.

Macroscopic Examination—This is the body of a white, female child about 15 months old. Only the front teeth, both lower and upper, are present. Body nourishment is fair. The chest is noticeably "barrel-shaped". The lower one third of the sternum is raised about 1 cm above the general level of the corpus sterni as the body lies on the table. The abdominal wall in front is slightly distended and rigid. The external genitalia and anus are unchanged. The skin of the face is hard, crusted and in places scaled (eczema?). The content of cranium is not examined (permission refused). Abdomen. The uterus and its appendages are markedly hyperemic. The diaphragm on the right side is pushed down to opposite the level of the fifth rib, the fifth interspace on the left. The lower level of the liver is 1 cm below the costal arch. The gallbladder is normally free. The urinary bladder is unchanged. The peritoneum is everywhere smooth and shiny. Thorax. The costal cartilages are soft. The lungs completely fill the pleural cavities. The lungs are free of adhesion. The pleura is everywhere smooth and shiny. There is no free fluid in the pleural sacs. The lungs and intact trachea from below the thyroid cartilage are removed en masse (weight 1677.5 gm), and put into 10 per cent liquor formaldehyd for later detailed study. Heart. The pericardial sac contains about 3 cc of clear fluid. The apex of the heart consists of right and left ventricles and in front the right ventricle is as broad as the left. The pulmonary artery contains only fluid blood. The pulmonary cusps are unchanged, as are the tricuspid leaflets. The right ventricle between base and apex is 1.5 cm thick. There is no change of the linings of the carotid arteries, the inferior vena cava and the aorta. The aorta is about two thirds the usual size and measures 12 mm in greatest diameter. Lymphoid tissue. The deep cervical lymph nodes are from 5 to 18 mm in diameter. They are firm, pale yellow and generally hyperplastic. The tonsils and the lymph nodules of the base of the tongue are about twice the normal size. Kidneys. The kidneys together weigh 62 gm. The cortical striations are well defined and the cortices are uniformly from 3 to 5 mm thick. They are grossly unchanged. Weights of organs. Suprarenals together, 5 gm; thyroid, 2.5 gm; thymus, 15 gm; spleen, 20.2 gm; pancreas, 7.5 gm; liver, 293.5 gm; heart, 57.5 gm.

Gross Description—The lobes of both lungs are distended by air (Fig 13), float high in water, and are soft and feathery to touch. The pleural surfaces

everywhere are smooth and shining and are grayish in color, except for a few scattered brownish slightly depressed, sharply defined, nodule-like areas measuring about 0.5 cm in diameter. There are some large emphysematous bullae in the apices and in the anterior margins of both lungs. The trachea and the main bronchi contain a small amount of mucopurulent tenacious exudate and their epithelial lining is reddened. The peritracheal and peribronchial lymph glands are conspicuous and their cut surfaces are reddish gray in color. The cut surfaces of all lobes of both lungs are dry, grayish red in color and are air filled except for the above described nodule-like areas which are distributed from the hilum to the pleural surface. The connective tissue septae throughout the lungs are conspicuous. A few of the medium sized and smaller bronchi are patent but most are almost or completely occluded by a grayish tenacious exudate and their walls appear thickened. The larger blood vessels especially in the lower lobes of both lungs are distended by blood.

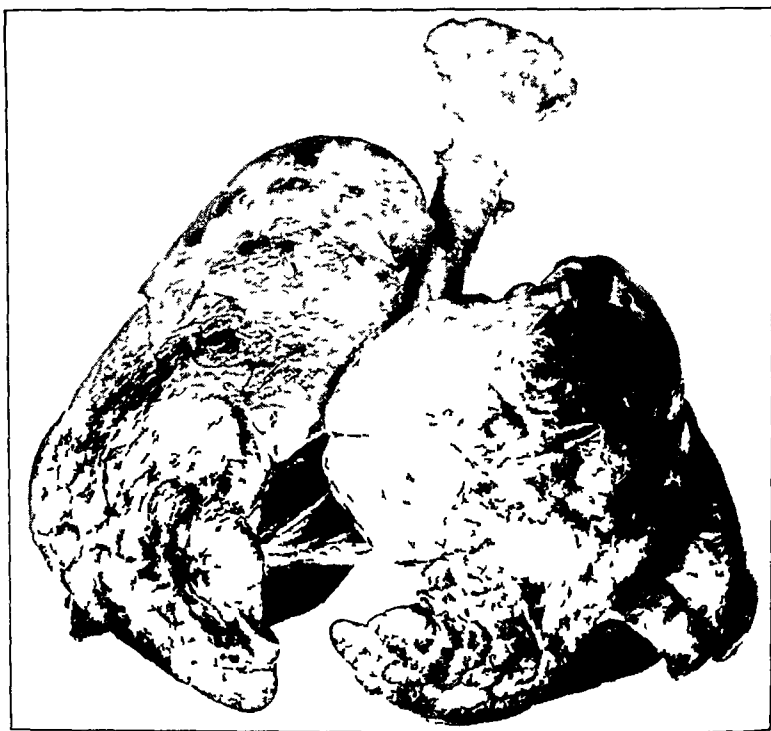


Fig 13—Case 6 Food asthma Infant Lungs showing acute emphysema

Microscopic Description—The structure of the different lobes of both lungs varies so little that a separate description of each is not necessary. The pleura throughout appears normal in structure and variations in thickness depend on the amount of air in the underlying tissue. Numerous connective tissue septa extending into the lung from the pleura are very conspicuous grossly and microscopically and sharply mark off definite units of lung tissue. These septa are composed of fibrous tissue which contains a few distended blood vessels and a few scattered lymphoid cells. There are also a few small collections of lymphoid cells beneath the pleura. The apices and anterior margins of both lungs are markedly emphysematous, the alveoli being widely distended and their walls thin and in places ruptured. The alveoli in the greater part of both lungs are air filled, moderately distended, and their walls of normal structure and thickness. The bronchioles and their finer divisions in these portions of the lungs are dilated and contain a more or less mucinous exudate in which there are varying numbers of polymorphonuclear neutrophil cells and

a few polymorphonuclear eosinophil cells. The epithelium is intact and is folded in only the contracted bronchioles. The basement membrane is not conspicuous. The subepithelial layer is relatively thin and contains only a few lymphoid cells and an occasional polymorphonuclear eosinophil cell. The muscle layer is scanty and irregular in distribution. The other connective tissue layer is thin and contains throughout numerous small definite lymphoid nodules with distinct germ centers.

The remainder of the lung tissue falls into two distinct groups which differ markedly from each other and from that already described. One of these is composed of definite areas from 0.5 to 1.5 cm in diameter which are sharply marked off by septa and are scattered irregularly throughout both lungs. The alveoli are small and almost completely filled by a fine granular precipitate containing a few polymorphonuclear neutrophil cells and a few red blood cells. The walls of these alveoli are thickened by distended capillaries. The bronchioles and their divisions are occluded by a mucous exudate containing many polymorphonuclear neutrophil cells, a few polymorphonuclear eosinophil cells and a few epithelial cells. The epithelium of the bronchioles is slightly thickened and the ciliated border is fused with the mucus in the lumen. The subepithelial layer is thin and contains a few round cells. The muscle layer is scanty and irregular in distribution. The outer connective tissue layer is increased in amount and in many bronchioles is infiltrated by lymphoid cells and polynuclear eosinophil cells which in some are grouped about blood vessels. Distinct lymph nodules are prominent in the walls of some of the bronchioles.

The other group of well defined areas are more scattered, air free, somewhat smaller in size and retain, as the only evidence of lung tissue, small contracted bronchioles whose lumina are completely occluded by a mucous exudate containing a few polynuclear neutrophile cells absorption atelectasis (Plate 2, D). The major portion of these areas consist of closely crowded small mononuclear cells, among which are a few small capillaries, fibroblasts large mononuclear cells (endothelial cells) and polymorphonuclear neutrophil and eosinophil cells. The blood vessels are small and are surrounded by an abnormal amount of fibrous tissue.

The small and medium sized bronchi in all parts of the lungs vary greatly in appearance and these variations seem to bear no definite relation to the abnormal lung tissue. Approximately two thirds of these bronchi are almost, or completely occluded by a mucous exudate (Plate 3, A) which contains varying numbers of polymorphonuclear neutrophil and eosinophil cells, a few desquamated epithelial cells, but no fibrin and showing in longitudinal sections distinct layer formation. The epithelium is intact, thrown into shallow folds and contains a few polymorphonuclear eosinophil cells. The outer ciliated border seems to fuse with the content of the lumina. The basement membrane is not prominent. The subepithelial layer is thin and contains only a few lymphoid cells and a few polymorphonuclear eosinophil cells. The muscle layer is thin and irregularly distributed. The mucous glands are very prominent, their acini large and separated from each other by a loose connective tissue containing only a few lymphoid cells and a few polymorphonuclear eosinophil cells. Outside the muscle layer the collections of polymorphonuclear eosinophil cells (Plate 3, B and C) usually surrounding moderately distended blood vessels, make a striking picture. The cartilages are of normal appearance. The outer fibrous tissue layer is prominent. The blood vessels are distended only in both lower lobes. The peribronchial nerves and nerve sheaths are not infiltrated by cells and are unchanged. The lymph nodes along all bronchi are very numerous and prominent and contain large germ centers with scattered cells, and their sinuses contain a few polymorphonuclear eosinophil cells. The remainder of the small and medium sized bronchi are widely dilated and contain small amounts of mucous exudate similar to that described above. The walls are similar in structure, except that they are thinner. In many sections, occluded and distended bronchi lie

side by side. The main and large bronchi contain varying amounts of mucus. Their walls except for the normal structural differences, are similar to the walls of the medium sized bronchi. The collection of polymorphonuclear eosinophil cells about small blood vessels between the muscle layer and the cartilages is very striking throughout the whole bronchial tree. The peribronchial lymph glands are numerous and very large. Their sinuses are distended and the germ centers prominent and all glands contain many eosinophil cells. A slight anthracosis is present. The thyroid, parathyroid, liver, pancreas, suprarenals and kidneys are normal in structure. The sinuses of the spleen are filled with blood and the splenic pulp contains large numbers of polynuclear eosinophil cells. The cervical and mesenteric lymph glands are large, the germ centers are prominent and have loosely arranged cells but no evidence of necrosis, and some contain many distended blood vessels. All lymph glands examined, except the mesenteric, contain many polymorphonuclear eosinophil cells. The thymus is well developed and the cortical portions contain many diffusely scattered, irregularly shaped, deeply stained cellular masses, Hassall's corpuscles. The cortical and medullary portions contain many groups of mononuclear eosinophil cells (Plate 3, D).

Comment—The chief pathologic findings in this infant may be summarized as follows: (1) complete occlusion of the majority of the middle sized and smaller bronchi by mucus. (2) Two distinct stages in the formation of areas which are interpreted as evidences of past asthmatic attacks (absorption atelectasis). (3) Extreme eosinophilia of the following structures: Bronchial wall, mucous content of bronchial lumen, mucous glands, spleen, lymphoid tissues and thymus. (4) Thickening of the walls of the bronchi and blood vessels. (5) Cell inclusions in the thymus. (6) Hypertrophy of entire lymphoid apparatus. (7) Narrowing of aortic arch. (8) Enlargement of the thymus.

The last three statements point to the possibility of this case being one of status lymphaticus, although the characteristic areas of necrosis in the lymph glands, which have been emphasized,²³ are absent. The clinical picture also is not characteristic.

The history of head colds and bronchitis preceding severe attacks is a point of interest. The history of eczema, of positive cutaneous tests for wheat proteins, of improvement in condition following the use of a wheat free diet and the lack of microscopic evidence of former infections in the subepithelial layer and in the mucous glands place this case in the category of the food asthmas.

MEASUREMENTS OF BRONCHI AND BRONCHIOLI

Since the abnormal inflation of the lungs and the impairment of respiration in asthma are undoubtedly associated with a narrowing of the lumina of the bronchial tubes, it is in order to ask what factors are involved in the production of this stenosis. Naturally, the attention is directed toward the smooth muscle fiber system, which acts by

23 Symmers, D. Status Lymphaticus, *Am J M Sc* 156 40, 1919

diminishing the size of the tube, and toward the exudative system (i. e., *a*, mucous epithelium, *b*, glands, and *c*, blood vessels and capillaries) which adds to the stenosis by its increase in size and in secretory activity. Both these systems, of course, are regulated in function by the nervous system.

If the bronchial muscle contracts, certain temporary changes in the structure of the walls must immediately occur, i. e., there must be an increase in the thickness of the muscle bundles and in the height of the epithelial folds. The question arises then whether repeated spasmodic attacks over a long period of time might not ultimately cause a true hypertrophy of the smooth muscle system as well as changes in other portions of the tubes. Previous workers noted that their cases seemed to show an increase in the thickness of the bronchial wall

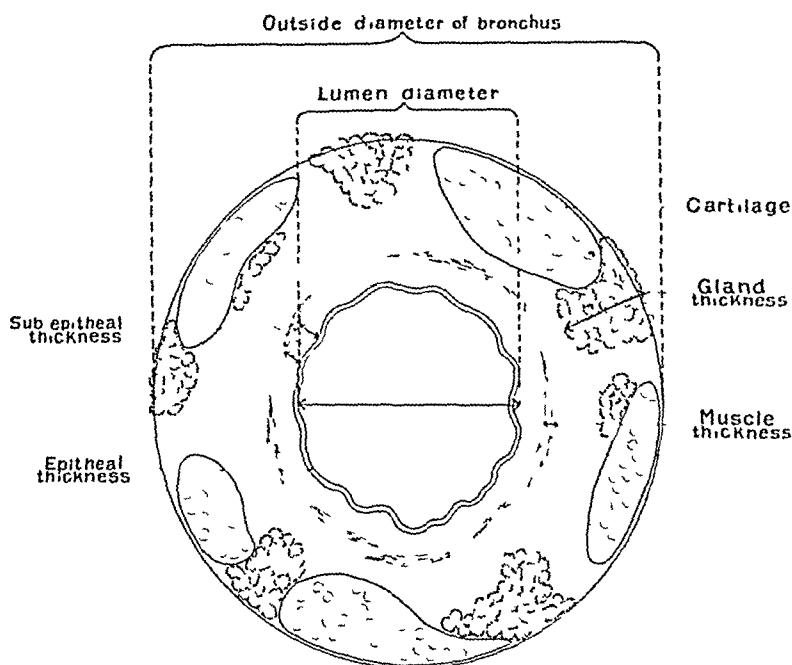


Fig 14—Diagrammatic view of the cross section of a bronchus to show the method used in making the measurements of the different structures

but to our knowledge no actual proof has yet been given for the existence of such a change. In order to obtain definite evidence on this important point, we have made a comparison of the measurements of the bronchial structures of asthmatic and nonasthmatic individuals.

The typical transverse sections of the bronchi and bronchioles on which histologic studies were made were measured microscopically with the micrometer, in the following manner: *a* = mean distance between outer borders, *b* = mean diameter of lumen, *c* = epithelial layer thickness, *d* = basement membrane thickness, *e* = subepithelial layer thickness, *f* = muscle bundle thickness, and *g* = mucous gland diameter (Fig 14). The classification of bronchi as to size is based on the measurement between outer borders and not on the diameter of the

lumen, as is usually done This method gives, we believe, especially in all cartilage-bearing tubes, a better basis for comparison than the usual method The measurement of the lumen takes into account the slight irregularities due to the shallow longitudinal epithelial folds The epithelial thickness is measured from the attachment of the cilia to the point of contact with the basement membrane The basement membrane thickness is measured only in those sections in which its borders are

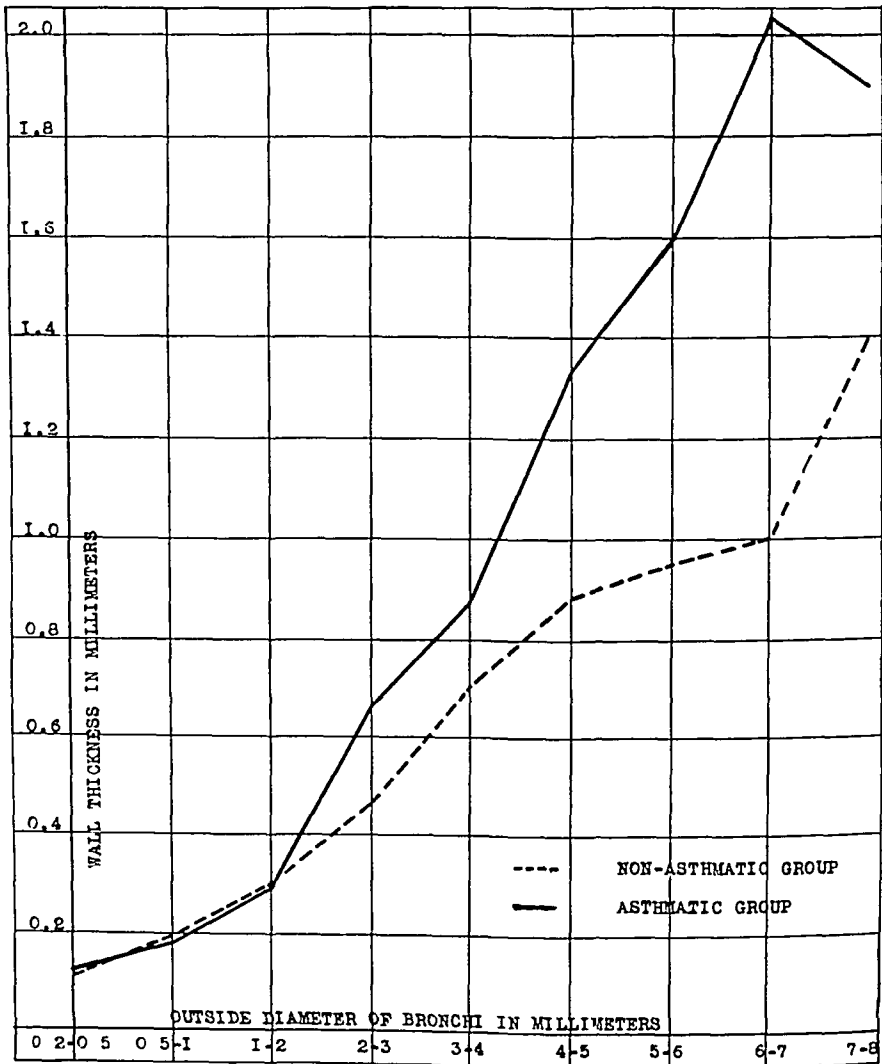


Fig 15—Graphs showing comparison of wall thickness

distinct The measurement of the subepithelial layer, which includes all tissues between the basement membrane and the muscle layer, also takes into account the longitudinal epithelial folds The diameters of the muscle bundles and of the mucous glands are measured at right angles to the tube lumen All measurements are made, as far as possible, in the tube segment with most uniform structures, otherwise the mean of several measurements is taken

Thirteen individuals, six asthmatic and seven nonasthmatic constitute our material on which the measurements of the bronchial structures were made. Some important data concerning them are given in Table 1.

TABLE 1 — DATA REGARDING INDIVIDUALS WHOSE BRONCHI WERE MEASURED

	Sex	Age	Death Due to	Chief Complaint
1 B	F	55 yrs	Suicide—drowning	Asthma
2 G	M	55 yrs	Asthma	Asthma
3 Le	M	29 yrs	Abscess of lung	Asthma
4 F L	M	29 (?) yrs	Acute fatal anaphylaxis	Asthma—horse
5 L	F	17 yrs	Acute streptococcus infection	Asthma
6 Baby A	F	15 mos	Asthma	Asthma
7 Gr	M	70 yrs	Cardiac decompensation	Chronic bronchitis
8 Br	F	62 yrs	Carcinoma of stomach	Carcinoma
9 A	M	50 yrs	Pneumonia of l. lower lobe	Chronic bronchitis
10 N L	M	27 yrs	Suicide, jugulars severed	Psychosis
11 R	M	26 yrs	Suicide, shot through heart	Psychosis
12 B	M	25 yrs	Brain abscess	Brain abscess
13 Baby N	F	15 mos	Enteritis	Enteritis

Numbers 7 and 9 are omitted from all graphs because of the questioned diagnosis of early asthma. Numbers 6 and 13 are also omitted from all graphs because of the youth of these patients, however, separate graphs, not reproduced here, show similar increased thickness in the tubes of the asthmatic child.

The measurements obtained from these subjects are given in Tables 2 and 3.

There are certain unavoidable apparent sources of error in the figures given in Tables 2 and 3 and in order to offset these the largest number of measurements possible are taken. Groupings by tube size is open to the objection that more measurements may be made near one extreme in one group than in the other, but our figures show that such occurrences influence the graphs about equally. Because of the marked variations in the size of the bronchi at the same distance from the bifurcation of the trachea in different persons, the criticism that the increase in wall-thickness in our asthmatic subjects may be due to a uniform contraction of all tubes cannot be answered definitely. The size and thickness of the bronchial cartilaginous plaques vary greatly, depending somewhat on nearness to a bifurcation, so that measurement of these plaques is of little value in determining location. However, the longitudinal folding of the epithelial layer, which may be one evidence of contraction, shows no consistent variation in the two groups of cases. It will be noted that tubes of the same size in the same individual show marked variations in structures but these are as striking in one group as in the other. Differences in numbers of measurements obtainable from different persons are unavoidable—the greatest numbers being obtained in those whose lungs furnished the greatest number of typical sections. The number of typical sections obtainable from each individual is limited by the amount of lung tissue originally obtained and the amount of tissue uninfluenced by other pathologic conditions such as pneumonia, etc.

TABLE 2—MEASUREMENTS IN MILLIMETERS OF BRONCHI
AND BRONCHIOLI ADULTS

These tables are arranged so that the outside diameter of the bronchial tubes is taken as the fixed standard of comparison. The differences in the size of structures of the asthmatic and non-asthmatic individuals as obtained from these measurements are demonstrated graphically in Figures 15, 16 and 17

Name	Diagnosis	Out side Diam eter	In side Diam eter	Wall Thick- ness	Epithe- lial Thick- ness	Base- ment Mem- brane Thick- ness	Sub Epithe- lial Thick- ness	Muscle Thick- ness	Gland Diam eter
Normal L	Normal	0.22	0.12	0.05	0.013		0.016	0.010	
Normal B	Brain abscess	0.28	0.18	0.05	0.016		0.013	0.0.0	
Mr E L	Asthma	0.28	0.18	0.05	0.025		0.010	0.016	
Miss L	Asthma	0.30			0.019		0.016	0.013	
Mr G	Asthma	0.32	0.14	0.09	0.016		0.036	0.026	
Mr G	Asthma	0.33	0.17	0.08	0.016		0.016	0.023	
Miss L	Asthma	0.35			0.022		0.016	0.012	
Normal L	Normal	0.36	0.14	0.11	0.010		0.007	0.010	
Normal L	Normal	0.36	0.12	0.12	0.016		0.033	0.020	
Mr E L	Asthma	0.36	0.12	0.12	0.039		0.028	0.028	
Mr E L	Asthma	0.38	0.14	0.12	0.023		0.028	0.021	
Normal B	Brain abscess	0.40	0.15	0.125	0.016		0.016	0.026	
Normal B	Brain abscess	0.42	0.10	0.16	0.016		0.016	0.020	
Mr R		0.44	0.28	0.08	0.013		0.013	0.013	
Mr G	Asthma	0.48	0.15	0.165	0.020		0.033	0.050	
Normal B	Carcinoma	0.50	0.21	0.145	0.013		0.019	0.013	
Normal B	Brain abscess	0.50	0.14	0.18	0.013		0.010	0.033	
Mr E L	Asthma	0.50	0.14	0.18	0.036		0.023	0.050	
Mr E L	Asthma	0.50	0.26	0.12	0.033		0.023	0.019	
Mr Gr	Bronchitis	0.50	0.22	0.14	0.013		0.020	0.033	
Normal B	Carcinoma	0.58	0.25	0.165	0.016		0.026	0.033	
Normal L	Normal	0.59	0.30	0.145	0.029		0.033	0.018	
Mr R		0.61	0.24	0.185	0.013		0.026	0.023	
Miss L	Asthma	0.64	0.10	0.27	0.033		0.023	0.019	
Mr R		0.64	0.22	0.21			0.023	0.019	
Mr R		0.67	0.24	0.215	0.033		0.026	0.026	
Normal L	Normal	0.68	0.30	0.19	0.025		0.042	0.025	
Mr R		0.70	0.24	0.23	0.033		0.033	0.037	
Mr Le	Asthma	0.70	0.20	0.25			0.042	0.016	
Mr R		0.71	0.30	0.205	0.021		0.023	0.026	
Mr R		0.71	0.26	0.225	0.033		0.050	0.049	
Mr R		0.71	0.31	0.20	0.013		0.033	0.033	
Mrs B	Asthma	0.71	0.40	0.155		0.0066	0.028	0.014	
Normal B	Brain abscess	0.80	0.52	0.14	0.018		0.021	0.021	
Normal L	Normal	0.80	0.60	0.10	0.019		0.016	0.019	
Mrs B	Asthma	0.86	0.60	0.13		0.0066	0.014	0.014	
Normal L	Normal	0.87	0.70	0.085			0.016	0.016	
Normal L	Normal	0.87	0.48	0.195	0.016		0.026	0.019	
Mr R		0.87	0.32	0.275	0.019		0.050	0.039	
Mr Gr	Bronchitis	0.88	0.66	0.11			0.056	0.042	
Normal L	Normal	0.91	0.40	0.255	0.052		0.042	0.042	
Mr G	Asthma	1.00	0.62	0.19	0.040		0.026	0.033	
Mrs B	Asthma	1.00	0.70	0.15		0.010	0.070	0.100	
Mrs B	Asthma	1.00	0.70	0.15		0.0066	0.028	0.014	
Mr R		1.00	0.53	0.235	0.013		0.066	0.039	
Mr R		1.10	0.50	0.30	0.033		0.033	0.040	
Normal B	Brain abscess	1.10	0.64	0.23			0.026	0.016	
Mr G	Asthma	1.12	0.62	0.25	0.026		0.033	0.0.6	
Normal B	Brain abscess	1.20	0.80	0.20	0.013		0.084	0.028	
Normal B	Brain abscess	1.20	0.80	0.20			0.070	0.028	
Mr R		1.28	0.63	0.325	0.023		0.083	0.050	
Normal L	Normal	1.40	0.86	0.270	0.025		0.070	0.019	
Mr G	Asthma	1.43	0.60	0.415	0.033	0.0066	0.040	0.037	0.17
Mr G	Asthma	1.60	1.16	0.22	0.045		0.056	0.033	0.18
Normal Br	Carcinoma	1.68	1.00	0.34	0.023		0.039	0.050	
Miss L	Asthma	1.80	1.10	0.35	0.050		0.050	0.033	
Normal Br	Carcinoma	1.80	1.16	0.32			0.033	0.033	
Mr A	Bronchitis	1.80	0.92	0.44			0.056	0.140	0.50
Normal Br	Carcinoma	1.84	1.16	0.34			0.033	0.033	
Mrs B	Asthma	1.90	1.50	0.20		0.010	0.015	0.043	
Normal L	Normal	1.95	1.25	0.35			0.056	0.040	0.46
Normal Br	Carcinoma	1.96	1.27	0.345			0.033	0.033	
Mrs B	Asthma	2.10	0.62	0.74		0.010	0.090	0.110	0.31
Mr F L	Asthma	2.10	0.92	0.59	0.060		0.058	0.150	
Mrs B	Asthma	2.20	1.30	0.45	0.033	0.012	0.042	0.042	0.30
Mr R		2.20	1.60	0.30			0.053	0.026	
Normal Br	Carcinoma	2.20	1.00	0.60	0.045	0.0066	0.070	0.070	0.24
Mr G	Asthma	2.28	1.16	0.56			0.0.0	0.054	
Mr A	Bronchitis	2.30	1.10	0.60		0.0099	0.100	0.140	0.50
Mr A	Bronchitis	2.40	1.00	0.70			0.120	0.180	0.28
Mrs B	Asthma	2.40	1.00	0.70			0.100	0.100	0.58
Mr G	Asthma	2.40	1.00	0.70	0.065		0.056	0.056	0.50

MEASUREMENTS IN MILLIMETERS OF BRONCHI									
ADULTS—(Continued)									
Name	Diagnosis	Out- side Diam- eter	In- side Diam- eter	Wall Thick- ness	Epithe- lial Thick- ness	Base- ment Mem- brane Thick- ness	Sub- Epithe- lial Thick- ness	Muscle Thick- ness	Gland Diam- eter
Mr E L	Asthma	2 40	1 10						
Miss L	Asthma	2 50	1 40	0 65					
Mrs B	Asthma	2 60	1 40	0 55	0 066	0 0072	0 056	0 056	0 26
Normal L	Asthma	2 70	1 70	0 20	0 084	0 0066	0 026	0 050	0 29
Miss L	Normal	2 70	1 60	0 50		0 010	0 043	0 043	
Mr Le	Asthma	2 70	1 20	0 55	0 033		0 052	0 026	
Mrs B	Asthma	2 80	1 80	0 80	0 084		0 026	0 056	
Mrs B	Asthma	2 90	1 50	0 55		0 0066	0 040	0 026	
Mr A	Bronchitis	3 00	1 46	0 75		0 012	0 140	0 056	0 36
Mr Le	Asthma	3 00	0 70	1 15			0 140	0 126	
Mr E L	Asthma	3 00	0 70	1 15		0 0099	0 070	0 086	0 32
Mrs B	Asthma	3 12	1 72	0 65			0 070	0 140	0 88
Mrs B	Asthma	3 20	1 40	0 70	0 083		0 140	0 180	0 72
Mrs B	Bronchitis	3 20	1 84	0 90		0 0072	0 180	0 200	0 50
Miss L	Bronchitis	3 33	1 68	0 68		0 010	0 100	0 110	0 36
Mr Gr	Asthma	3 33	1 74	0 825	0 058	0 0072	0 100	0 180	0 37
Mr Gr	Asthma	3 40	1 80	0 795		0 0072	0 070	0 086	0 86
Mrs B	Bronchitis	3 40	1 30	0 80			0 054	0 066	0 48
Mr A	Carcinoma	3 42	1 56	1 05			0 070	0 084	0 28
Normal Br	Asthma	3 50	1 40	1 05	0 078		0 045	0 039	0 34
Mr G	Asthma	3 50	1 75	0 93			0 056	0 070	0 29
Mrs B	Asthma	3 50	1 94	0 875	0 056		0 083	0 110	0 40
Normal L	Asthma	3 60	1 80	0 78	0 070		0 110	0 160	0 86
Normal L	Asthma	3 80	1 75	0 90	0 056	0 0066	0 085	0 220	0 14
Normal L	Asthma	4 00	2 60	1 025		0 010	0 040	0 070	0 38
Mrs B	Normal	4 00	1 90	0 60	0 045		0 100	0 140	0 34
Mr Gr	Normal	4 00	3 00	1 05	0 050		0 100	0 100	0 90
Mr Gr	Asthma	4 20	3 00	0 50	0 010		0 084	0 095	0 30
Mrs B	Bronchitis	4 20	2 28	0 50	0 033		0 100	0 120	0 20
Mrs B	Bronchitis	4 50	1 80	0 96	0 039		0 100	0 180	0 70
Mrs B	Asthma	4 50	1 20				0 033	0 042	0 30
Normal B	Asthma	4 64	2 40	1 05	0 010		0 110	0 060	0 32
Normal Br	Asthma	4 80	2 80	0 92	0 056		0 170	0 054	0 44
Miss L	Brain abscess	4 80	2 24	0 92	0 050	0 0066	0 120	0 200	0 70
Normal L	Carcinoma	5 00	0 86	1 28			0 090	0 120	0 80
Mrs B	Asthma	5 04	3 50	1 97			0 100	0 180	0 60
Mr Gr	Normal	5 06	3 14	0 75			0 100	0 140	0 86
Mrs B	Asthma	5 10	2 50	0 95			0 220	0 130	0 58
Mr Gr	Bronchitis	5 44	3 20	1 28	0 042		0 096	0 200	1 10
Mr G	Asthma	5 60	1 92	0 95	0 063	0 0066	0 066	0 090	0 30
Mr Gr	Bronchitis	5 76	2 54	1 96	0 056		0 100	0 072	0 70
Normal L	Asthma	6 00	2 40	1 53			0 115	0 140	0 72
Normal L	Bronchitis	6 08	3 50	1 68			0 260	0 084	0 32
Mrs B	Normal	6 40	4 08	1 25			0 200	0 260	1 00
Mrs B	Asthma	6 50	3 30	1 00	0 071	0 0066	0 220	0 200	0 71
Mrs L	Asthma	6 50	5 00	0 75	0 062	0 0099	0 120	0 180	1 00
Mr G	Asthma	6 50	4 00	1 25	0 050		0 120	0 190	1 00
Miss L	Asthma	6 50	2 70	1 95	0 036		0 230	0 200	0 72
Mr Gr	Asthma	7 00	2 52	1 95	0 052		0 100	0 110	0 62
Normal B	Asthma	7 15	3 95	2 24			0 115	0 140	0 38
Normal Br	Bronchitis	7 30	4 92	1 60	0 013		0 110	0 056	0 18
Mr R	Brain abscess	7 50	3 00	1 19	0 010		0 110	0 110	1 10
Normal B	Brain abscess	7 50	2 25	1 65	0 056	0 0066	0 210	0 180	1 10
Mrs B	Carcinoma	8 00	4 20	1 25	0 056		0 130	0 220	0 33
Mrs B	Brain abscess	8 00	5 50	1 25	0 056	0 0066	0 157	0 140	0 60
Mr G	Asthma	8 40	5 00	1 50	0 066	0 0066	0 140	0 240	1 00
Mr Gr	Asthma	8 40	5 72	1 60	0 050		0 070	0 150	0 71
Mr Gr	Asthma	8 50	5 50	1 34	0 056	0 0066	0 112	0 126	0 58
Normal B	Bronchitis	8 50	5 00	1 50	0 056	0 0066	0 110	0 090	0 30
Mr A	Asthma	9 20	5 00	1 75	0 056		0 042	0 120	0 50
Mr G	Brain abscess	9 00	5 20	1 75	0 033	0 0050	0 070	0 120	0 53
Normal L	Bronchitis	9 50	4 50	2 50	0 050	0 010	0 070	0 120	0 74
Mr Gr	Asthma	10 00	5 50	2 25	0 011	0 0066	0 200	0 200	1 20
Mr Gr	Normal	10 00	6 00	1 75	0 0099	0 0066	0 12	0 160	0 33
Mr A	Bronchitis	11 00	6 50	2 00	0 0066		0 120	0 140	0 88
Mr Gr	Bronchitis	11 00	6 50	2 25	0 084	0 020	0 090	0 070	0 72
Miss L	Bronchitis	12 00	6 00	2 25	0 070	0 120	0 190	0 58	
	Bronchitis	12 00	7 00	3 00	0 120	9 240	0 256	0 31	
	Asthma	12 00	6 50	2 50	0 200	0 180	0 250	0 80	
		8 50	2 75	0 064	0 200	0 250	0 350	0 88	
		1 75		0 071	0 0066	0 022	0 140	1 20	
					0 0099		0 240	0 72	
					0 0066				

TABLE 3—MEASUREMENTS IN MILLIMETERS OF BRONCHI AND BRONCHIOLI INFANTS

Name	Diagnosis	Out- side Diam- eter	In side Diam- eter	Wall Thick- ness	Epithe- lial Thick- ness	Base- ment Mem- brane Thick- ness	Sub- Epithe- lial Thick- ness	Muscle Thick- ness	Gland Diam- eter
Infant A	Asthma	0.38	0.18	0.10	0.016			0.007	
Infant N	Enteritis	0.38	0.20	0.09	0.013		0.007	0.010	
Infant N	Enteritis	0.50	0.38	0.06	0.016		0.013	0.010	
Infant A	Asthma	0.66	0.36	0.15	0.033		0.070	0.056	
Infant N	Enteritis	0.72	0.46	0.13	0.026		0.016	0.013	
Infant A	Asthma	0.92	0.62	0.15			0.019	0.010	
Infant N	Enteritis	0.94	0.50	0.22	0.040		0.020	0.017	
Infant A	Asthma	1.00	0.46	0.27			0.016	0.016	
Infant N	Enteritis	1.18	0.86	0.18	0.050		0.033	0.017	
Infant A	Asthma	1.40	1.00	0.20			0.028	0.042	
Infant A	Asthma	1.40	0.50	0.45	0.036		0.033	0.016	
Infant N	Enteritis	1.54	0.86	0.34	0.050		0.033	0.017	
Infant A	Asthma	1.60	0.88	0.36			0.033	0.020	0.20
Infant N	Enteritis	1.80	1.00	0.40	0.050		0.025	0.025	
Infant N	Enteritis	1.80	1.00	0.40	0.050		0.027	0.020	
Infant A	Asthma	2.20	1.20	0.50			0.066	0.033	0.20
Infant A	Asthma	2.20	1.00	0.60	0.040		0.070	0.024	0.36
Infant A	Asthma	2.20	1.40	0.40			0.070	0.042	
Infant A	Asthma	2.40	1.10	0.65			0.084	0.042	0.22
Infant A	Asthma	2.40	1.60	0.40	0.039		0.10	0.023	0.20
Infant N	Enteritis	2.40	1.56	0.42	0.042		0.042	0.023	0.14
Infant N	Enteritis	2.56	1.56	0.50	0.042		0.056	0.042	0.28
Infant A	Asthma	2.60	1.3	0.65	0.033		0.084	0.042	0.42
Infant A	Asthma	2.64	1.36	0.64	0.033		0.084	0.019	0.36
Infant N	Enteritis	2.68	1.54	0.57	0.040		0.013	0.013	0.28
Infant A	Asthma	3.00	1.8	0.60			0.046	0.026	0.42
Infant A	Asthma	3.40	1.4	1.00	0.029	0.066	0.157	0.042	0.30
Infant A	Asthma	4.50	2.4	1.05	0.026		0.140	0.10	0.70
Infant N	Enteritis	5.50	3.5	1.00	0.013	0.0066	0.084	0.146	0.30
Infant A	Asthma	5.60	2.40	1.60	0.033	0.0066	0.142	0.10	0.72
Infant A	Asthma	6.50	2.50	2.00	0.046	0.0066	0.10	0.056	0.42
Infant A	Asthma	7.50	3.50	2.00	0.042		0.070	0.034	0.58
Infant N	Enteritis	7.50	4.50	1.50	0.036		0.070	0.120	0.58

Figure 15 shows graphically the differences in wall thickness in the asthmatic and nonasthmatic subjects. Figures 16 and 17 show graphically the differences in the subepithelial layer and the muscle bundle thickness in the same groups of subjects. The increase in the wall thickness in asthmatics is accounted for only in part by the increased size of the subepithelial layer and of the muscle bundles. Measurements show, however, that the mucous glands in most of our asthmatic subjects are considerably enlarged, and as this gland system is present inside, outside and between the edges of the cartilaginous plaques, no adequate system of measurement could be devised to determine the actual increase due to gland changes. We recognize also the change produced by hyperemia in the tissues between the cartilages and muscle bundles, but this change is difficult to determine by measurements because of the influence of glandular changes. The tubes with an outside diameter of less than 2 mm show in the graphs only a slight variation in thickness, the asthmatic group showing somewhat smaller measurements probably due to the influence of emphysema. The thickness of epithelium, subepithelial layer and muscle bundles in

divisions of the tubes below the bronchioli are practically the same in the two groups

A great deal of caution must be observed in the interpretation of epithelial fold formation as evidence of abnormal bronchial contraction, as deep folds are frequently found postmortem in apparently normal bronchi and bronchioli much like the folding of the intima in arteries

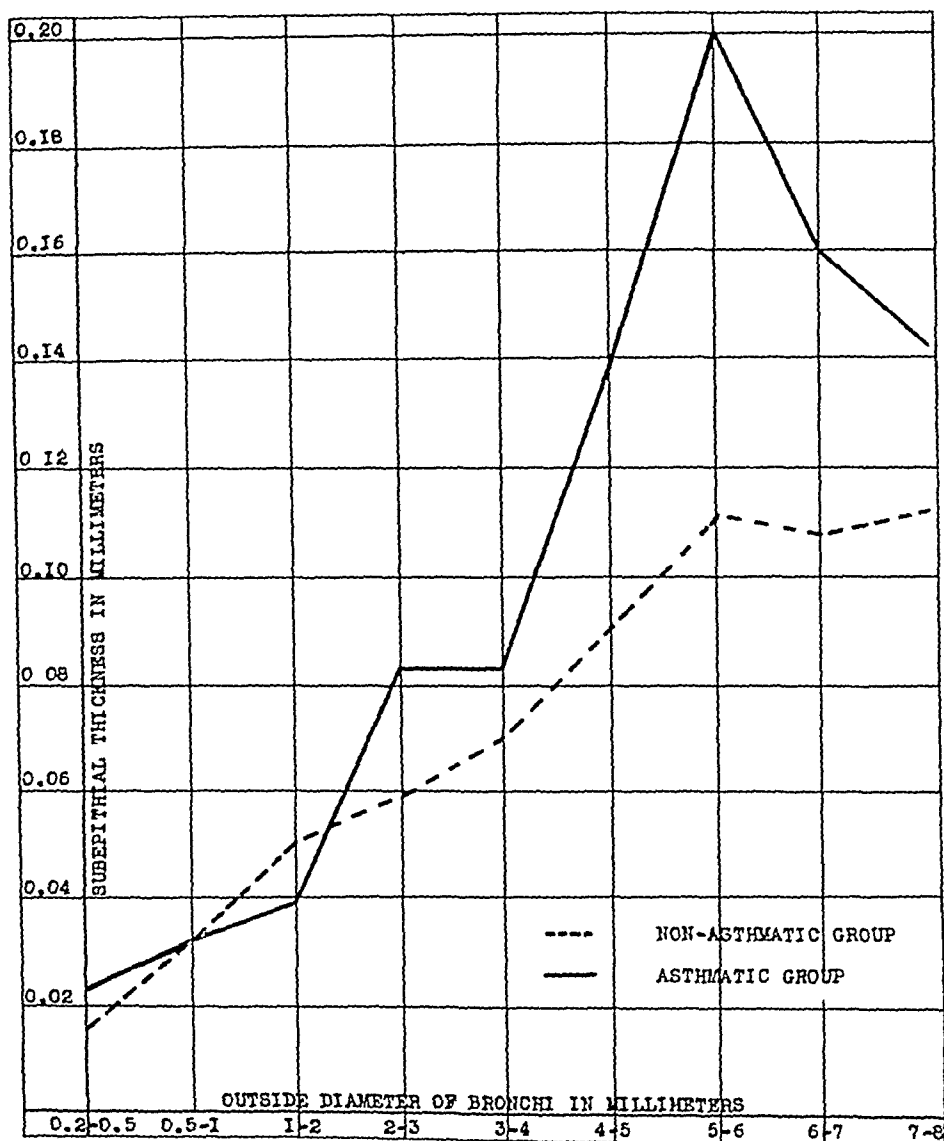


Fig 16—Graphs showing comparison of subepithelial thickness

We have examined the bronchi and bronchioli of many persons who died of various disorders and have gained the impression that the epithelial folding, when present in asthmatics, is of a greater degree than that found in nonasthmatic (Cases 2 and 4) The amount of variation is of about the same degree as that found in the normal and in the anaphylactic guinea-pig lung Pictures like those shown in Figures 18 and 19 are not usually seen in the lungs of normal guinea-pigs when the animal is killed by a stroke on the head It is just such

pictures, in addition to the therapeutic (inhibitive) effect of epinephrin and atropin, which form the chief evidence for the bronchospastic origin of the acute emphysema of the anaphylactic shock in the guinea-pig. While asthma is a chronic condition and is frequently accompanied by varying degrees of emphysema, the acute paroxysmal attack is the

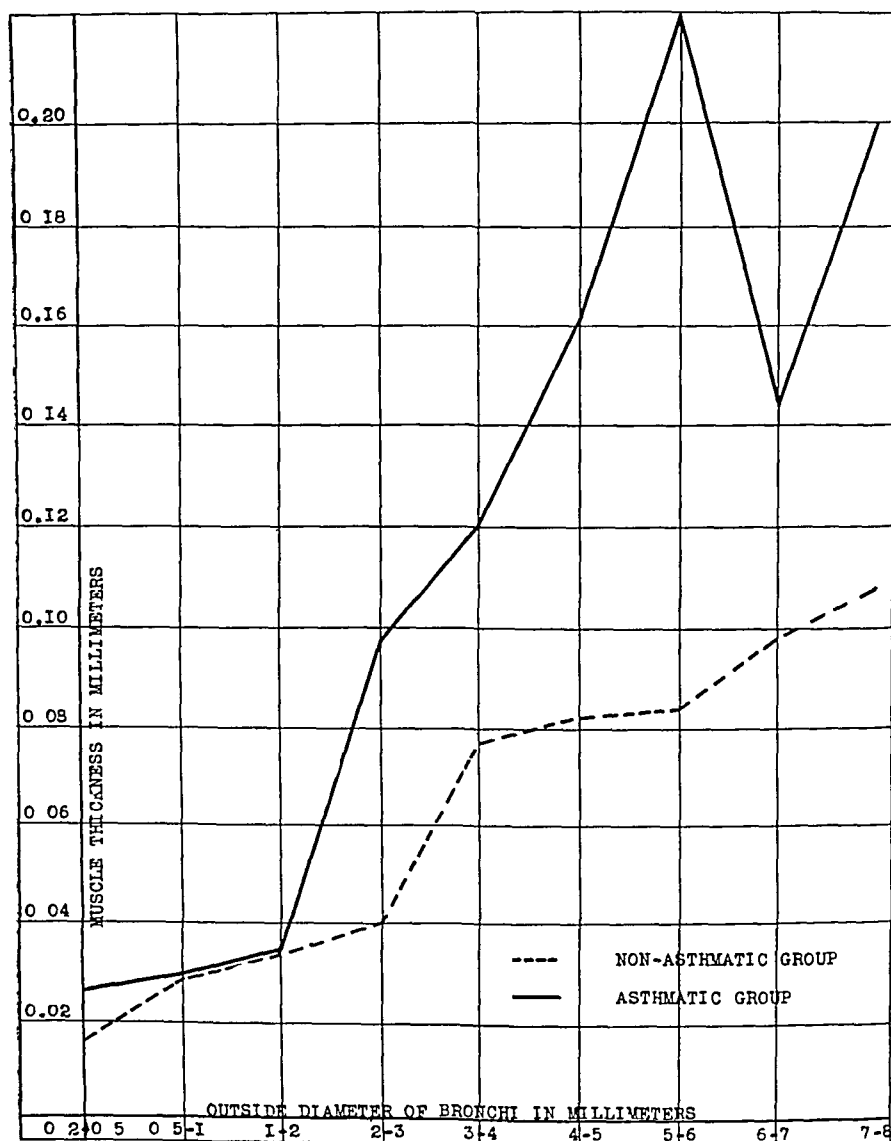


Fig 17—Graphs showing comparison of muscle thickness

main characteristic symptom of the disease, and when associated with an acute stage of emphysema it forms the equivalent to the anaphylactic shock. In three of our cases (Cases 2, 3 and 4) the lumina of many small bronchi and bronchioles are almost occluded by folded epithelium (Plate 2, A and B, Fig 9). The marked folding of the epithelium in our other cases is present but is not so striking as in the three cases cited.

TABLE 4—GENERAL SUMMARY OF CLINICAL DATA OF ALL CASES

Case	Reported by	Date	Age	Sex*	Occupation	Duration	Heredity	Associated Disorders	Cause of Death
1	v Leyden	1886	40	♀		From childhood	Not reported		Died during an attack
2	Berkart	1889	37	♀		14 yrs	Not reported		Died during an attack
3	F Schmidt	1892	49	♀	Waitress	23 wks	Not reported	Carcinoma in mediastinum, articular rheumatism	Died during an attack
4	A Fraenkel	1898	63	♂	Carpenter	9-10 mos	Not reported	Rheumatism, gout, bronchial catarrh (3 yrs)	Died during an attack
5	A Fraenkel	1900	48	♂	Not reported	At least 20 mos	Not reported		Died during an attack
6	Jezierski	1905	63	♂	Gardener	Probably about 4 yrs	Father had asthma	Pneumonia	Pneumonia
7	Jezierski	1905	46	♀	Silk-weaver	12 yrs	Not reported		Died during an attack
8	Ellis	1908	27	♂	Coachman	At least 1 yr	Not reported	Tachycardia	Died during an attack
9	Monckeberg	1909	29	♂	Mason	3 yrs	Not reported	Pneumonia at 12 and 18, psoriasis, anasarca	Died during an attack
10	H Heizer	1911	2			After 9th month	Negative	Eczema	Died during an attack
11	Tichmeneff	1913	29	♀	College student	From childhood	Not reported	Croup, nasal catarrh	Duodenal hemorrhage
12	Marchand	1915	53	♀		23 yrs	Mother had asthma and bronchitis	Bronchitis since 17th year	Died during an attack
13	Marchand	1915	45	♀		At least 1 yr	Not reported		Died during an attack
14	Marchand	1918	48	♂	Chemical worker	2 yrs	Aunt had asthma		Died during an attack
15	Kamehorn and Ellis	1921	52	♂	Actor and fish-monger	From childhood	Father, father's mother, 1 uncle, 1 aunt and 1 child had asthma		Heart failure
16	Huber and Koessler	1922	55	♀	Musician, housewife	5 yrs	Negative	Bronchitis and coryza	Suicide by drowning
17	Huber and Koessler	1922	55	♂	Real estate	6 yrs	Mother, 2 sisters, 1 brother and 1 child had asthma	Bronchitis	Died during an attack
18	Huber and Koessler	1922	17	♀		From childhood	Negative		Pericarditis and peritonitis
19	Huber and Koessler	1922	29	♂	Soldier	19 yrs	Mother had asthma	Head colds	Fatal anaphylaxis
20	Huber and Koessler	1922	32	♂	Car repairer	From childhood	Negative		Abscess of lung, pneumonia
21	Huber and Koessler	1922	15 mo	♀		5 mos	Negative	Eczema, undernourished	Died during an attack

* In this column, ♂ indicates male, and ♀ female

The increased thickness of the muscle layer of the bronchi in all of the cases reported is apparent from our measurements. The muscular tissue is well developed, not only in the middle sized and small bronchi but even in the bronchioli. This increase in the size of the smooth muscles surrounding the bronchi may be due to a true increase in the size and quantity of the muscle cells, therefore a true hypertrophy, or it may be due to an increased contraction of the muscle. Increased contraction of a smooth muscle implies with few exceptions²⁴ increased muscular tonus and the increased thickness of a smooth muscle due

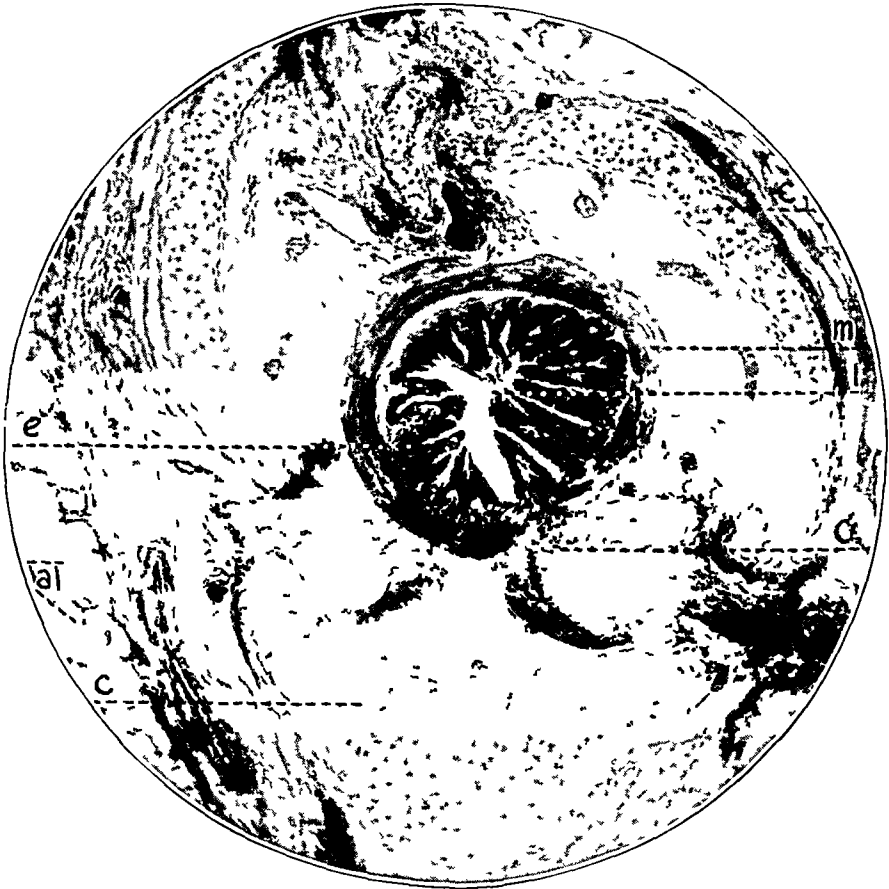


Fig 18—Guinea-pig Fatal horse serum anaphylaxis. Large bronchus. Cross section. Epithelium deeply folded and almost obliterating the lumen. Muscle layer forms a distinct layer. There are no glands. *l*=lumen, *e*=epithelium, *m*=muscle, *c*=cartilage, *al*=alveoli. Magnification, 70 diameters.

to contraction is the morphological expression of hypertonus. These factors—hypertonus, repeated contraction, and hypertrophy are closely and functionally related and probably all three are involved in the production of the increased thickness of the muscle tissue in the bronchi of the asthmatic.

²⁴ Bayliss. General Physiology, p. 538.

The deductions which are permissible from the data obtained by than 2 mm outside diameter is greater in the asthmatic group (2) these measurements are (1) The wall thickness of tubes of more This difference is due to increased thickness of the subepithelial layer, of the muscle bundles and of the tissues outside the muscle bundles

TISSUE EOSINOPHILIA IN BRONCHIAL ASTHMA

Of the cellular elements found in the bronchial secretory system and its product, the sputum, the most interesting are the eosinophil

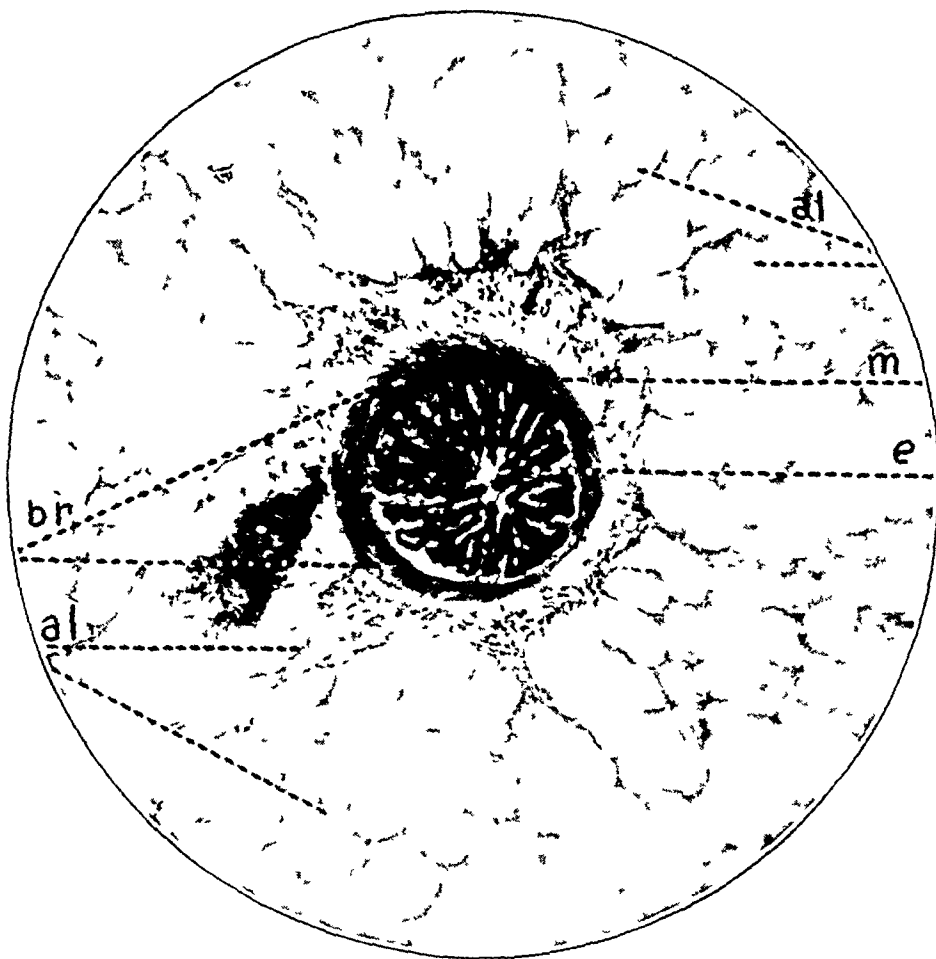


Fig 19—Gunea-pig Fatal horse serum anaphylaxis Bronchiole Cross section Lumen obliterated by folded epithelium *e* = epithelium, *m* = muscle, *al* = alveoli Magnification, 90 diameters

cells Their numerical increase in the circulating blood and their predominance in the sputum during the attack have been considered for many years a characteristic clinical symptom of asthma Since the diagnostic value of this finding has been questioned, various observers reporting that in other diseases of the lungs and bronchi an increased number of eosinophils is present in the sputum,²⁵ we wish to state that

25 Von Hoesslin, H Das Sputum, Berlin, Springer, 1921, pp 114-120

TABLE 5—GENERAL SUMMARY

Case	Macroscopic Description	Content of Lumen of Bronchi	Epithelium	Basement Membrane	Subepithelial Layer
1 v Leyden (1886)	Marked vesicular emphysema, bronchial mucosa reddened, small bronchi partially occluded by mucous masses	Small bronchi partially occluded, Mucus adherent to epithelium			
2 Berkart (1889)	Right apical adhesions, lungs emphysematous, masses almost occlude right main bronchus and one branch of left, smaller bronchi dilated and partially occluded, heart dilated and hypertrophic, moderate ascites	Masses composed of degenerating cylindrical epithelium, small bronchi contain detritus and fragments of Charcot Leyden's crystals	Almost all denuded, one deep ulcer extends almost to cartilage		
3 Schmidt (1892)	Tumor masses in left side of neck and extending into anterior mediastinum and upper lobes of both lungs, bilateral apical adhesions, lungs contain much blood, small bronchi contain masses of mucus	Many bronchi almost occluded by masses containing cells, these masses form spirals	Well retained		Much dense CT infiltrated by round cell
4 Fraenkel (1898)	Right apical adhesions, lungs emphysematous, nodular hypertrophy in lower lobe, bronchi contain masses which can be pulled out thread like walls of bronchi thickened, dilation of right and left ventricles	Mucous masses contain twisted threads, and epithelial cells which are greatly elongated, eosinophils	High grade desquamation		Thickened
5 Fraenkel (1900)	Middle sized and small bronchi occluded by screw shaped clots	Mucous masses completely occluding many bronchi and made up of layers containing elongated epithelium and eosinophil cells	Cells in small bronchi greatly elongated		Groups of leukocytic cells, many eosinophil cells
6 Jezierski (1905)	Right lung pneumonic, bronchi of left dilated, mucosa hypertrophic	Middle-sized and small bronchi of left partly occluded by mucus containing desquamated epithelium, neutrophils, eosinophils and lymphocytes	Fairly retained and infiltrated by round cells		Infiltrated by round cells, tissue increased, many engorged blood vessels
7 Jezierski (1905)	Fluid in both pleural cavities, left lung emphysematous	Small bronchi of left occluded by mucous plugs containing elongated epithelial cells, round cells, eosinophil cells	Mostly intact	Interrupted by accumulations of round cells	Contain many round cells
8 Ellis (1908)	Lungs emphysematous right adhesive pleuritis many bronchi occluded by greenish colored mucus	Most of smaller bronchi occluded by mucous plugs containing some degenerated epithelial cells, neutrophils and a few eosinophils, mucous plugs show spiral arrangement	Mostly intact in smaller bronchi, desquamated in larger	Hyalinized in the larger bronchi	Contains many polymorphous cells, some being eosinophil cells
9 Monckeberg (1909)	Ascites, anasarca, bilateral adhesive pleuritis, mediastinal and peribronchial lymph glands enlarged, lungs air filled, walls of bronchi thickened, lumen of most of smaller bronchi occluded by mucus, right heart enlarged, aorta narrowed	Small bronchioles empty, larger bronchioles occluded by mucous plugs containing desquamated epithelial cells and round cells, mucus shows spiral arrangement, Charcot Leyden's crystals in larger bronchi	Mostly intact	Hyalinized and thickened in larger bronchi	Infiltrated by round cells and many eosinophil cells, contain diverticula like protrusion of epithelium
10 H Heizer (1911)	Lungs distended, many bronchi almost occluded by mucus right ventricle thickened	Contains leukocytes and epithelium			Thickened by infiltrating cells and distended capillaries
11 Tchumeneff (1913)	500 cc fluid in left pleural cavity, left adhesive pleuritis, cavity in left upper lobe mucopus in bronchi, ulcer in duodenum	Mucus containing round cells and leukocytes in many bronchi	Greatly elongated, hyperplasia		Thickened, marked round cell infiltration
12 Marchand (1915)	Lungs emphysematous, occlusion of many small bronchi, slight hypertrophy of right heart	Plugs in bronchi composed of epithelium, round cells and crystals	Contains many goblet cells, infiltrated by cells		Infiltrated by round cells, some eosinophil cells

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Muscle	Mucous Glands	Fibrocartilaginous Layer	Blood Vessels	Nerves	Alveoli	Lymph Glands	Other Tissue
	Mucous glands small and atrophic				Some dilated, most filled by a granular material containing many large cells		
	Mucous glands in active secretion		Periarteritis obliterans in vessels of upper lobe		Emphysematous, some contain a fibrinous exudate		
		Thickened, infiltrated by round cells	Extremely dilated in mucosa of bronchi		Some dilated and some filled by mucus, no spirals, broncho-pneumonic areas about some bronchi	Large and pigmented	
Eosinophil cells between muscle bundles	Marked cellular infiltration, many eosinophil cells in glands		Bronchial capillaries markedly distended		Patchy emphysema, alveoli contain a few eosinophil cells		
		Contains many round cells	Many new-formed engorged blood vessels in walls of bronchi	Phrenic nerve contains degenerating fibers		Numerous groups of round cells in wall of bronchi	
		Contains many round cells	Surrounded in many cases by round cells		No change	Bronchial glands anthracotic	
Not changed	Contains many mononuclear cells, some being eosinophil cells		Vessels in bronchial wall engorged by blood		Many distended, some contain many eosinophil cells		Not changed
Increased in alveolar septae, increased in bronchi and larger bronchioles	Large	Contains many mononuclear and polynuclear cells	Pulmonary artery sclerotic, pulmonary veins thickened		Some occluded by granular precipitate	Prominent lymphoid nodules in larger bronchi	
	Greatly enlarged and filled by mucus		Distended		Some distended	All enlarged	
Hypertrophied, infiltrated by round cells	Enlarged, infiltrated by round cells				Some contain leukocytes		
Infiltrated by round cells	Contain many round cells					Distinct nodes formed in walls of middle sized and smaller bronchi	

TABLE 5—GENERAL SUMMARY—

Case	Macroscopic Description	Content of Lumen of Bronchi	Epithelium	Basement Membrane	Subepithelial Layer
13 Marchand (1915)	Pulmonary emphysema, some bronchi almost occluded by exudate, bronchial mucosa swollen and reddish, peribronchial lymph glands enlarged	Arranged in layers and contains many polynuclear leukocytes, a part contain strands of fibrin	Well retained a few goblet cells	Thickened and hyalinized	Contains many eosinophil cells, some lymphoid cells and a few polynuclear leukocytes
14 Marchand (1918)	Lungs distended, smaller bronchi occluded by yellowish masses left antrum of Highmore filled by secretion, walls of right and left ventricle thickened	Mucous masses in bronchi contain leukocytes, round cells and eosinophils, mucus forms spirals in smaller bronchi			Capillaries engorged, infiltrated by cells, many eosinophil cells
15 Kamachorn and Ellis (1921)	Left adhesive pleuritis, all other serous cavities contain fluid left lung collapsed, right upper and middle lobes distended tenacious mucus in middle sized bronchi, hypertrophy of right ventricle	Mucus contains epithelial cells, leukocytes and a few eosinophil cells and is arranged in spirals	Mostly desquamated		Capillaries engorged, infiltrated by mononuclear cells
16 Huber and Koessler (1922)	Coroner's inquest, report not available lungs distended most bronchi, except larger, occluded by mucous masses	Mucous masses in bronchi contain desquamated epithelium, round cells, neutrophil and eosinophil leukocytes, mucus in layers and twisted, some bronchioles contain many eosinophil cells	Partially desquamated	Thick and hyalinized	Infiltrated by many round cells and a few eosinophil cells
17 Huber and Koessler (1922)	Emphysema of lungs, bronchi contain a small amount of mucus	Mucus in small bronchi is scanty and contains only a few epithelial cells	Mostly intact	Not conspicuous	Not uniformly thickened contains many dilated capillaries
18 Huber and Koessler (1922)	Peritonitis, right adhesive pleuritis pericarditis, small amount of mucus in smaller bronchi	Small amount of mucus containing a few epithelial cells and a few eosinophils	Mostly intact goblet cells numerous in large bronchi	Thick and hyalinized	Infiltrated moderately by cells, some eosinophil
19 Huber and Koessler (1922)	Right fibrous pleuritis, marked emphysema cut surface of lungs dry	Smaller bronchi contain a granular precipitate	Mostly intact, many goblet cells	Thick and hyalinized	Cellular infiltration marked
20 Huber and Koessler (1922)	Abscess of left lung pulmonary emphysema, pneumonia of right lung bronchial walls thickened, hypertrophy of right heart	Contains fragments of epithelium and neutrophil leukocytes	Partially desquamated	Indistinct	Markedly infiltrated by mononuclear cells
21 Huber and Koessler (1922)	Moderate emphysema of both lungs small firm nodules in both lungs, some bronchi occluded by mucus lymph glands large	Contains fragments of epithelium, neutrophil and eosinophil cells	Mostly intact, some goblet cells	Not conspicuous	Contains a few round cells and eosinophil cell

on the basis of the examination of several hundred patients suffering from true bronchial asthma and other respiratory disease associated with dyspnea, we can say that the coincidence of sputum and blood eosinophilia in the same individual seems to be a pathognomonic symptom of the asthmatic state. Exceptions to this statement are pulmonary distomatosis and hydatid disease.

In our work we are mainly concerned with the local accumulation of eosinophil cells in the tissues of the bronchi a localization which has

—OF PATHOLOGY OF ALL CASES—(Continued)

Muscle	Mucous Glands	Fibrocartilaginous Layer	Blood Vessels	Nerves	Alveoli	Lymph Glands	Other Tissue
Tissue between muscle bundles contains round cells and some eosinophil cells	Large cells filled by mucus, gland duct epithelium contains many goblet cells	Contains many lymphoid cells	Distended and many contain numerous polynuclear neutrophils		Some areas completely consolidated	Some small lymph nodules contain a few eosinophil cells	
Hypertrophied	Enlarged		Sclerotic		No change	One contains a small tubercle	
No change							
Thickened	Enlarged, structure altered by many foci of round cells, infiltrated by eosinophil cells	Some cartilages calcified	No change	No changes	Irregular in size	Anthracotic	
Thickened	Small, contain many foci of round cells and areas of areolar tissue, ducts form distinct ampullae	No change	Walls of bronchial arteries thickened	No changes	Irregular in size, some contain a granular precipitate	Anthracotic	No changes
Thickened, forms a distinct ring in some bronchioles	Large and containing many foci of round cells, gland ducts form distinct ampullae	Ossified cartilages	Walls of bronchial arteries moderately thickened	No changes	Vary in size	No changes	No changes
Not prominent	Small and densely infiltrated by round cells	Calcified and ossified cartilages	Walls of bronchial arteries markedly thickened	No changes		No changes	Spleen contains many eosinophil cells
Structure altered by round cell infiltration	Small, ascini separated and composed of compact masses of cells	Calcified areas in cartilages	Walls of bronchial arteries thickened	No changes	Patchy obliteration of alveoli, these areas contain hyperplastic epithelium	No changes	No changes
Eosinophil cells between muscle bundles	Enlarged, contain foci of round cells and eosinophil cells	Many eosinophil cells between cartilages and muscle layer	Walls of bronchial arteries thick	No changes	Obliterated in patches by pneumonic foci	No changes	Spleen and thymus contain many eosinophil cells
				Some areas of absorption atelectasis	Contain eosinophil cells		

been previously observed by others This tissue eosinophilia is a phenomenon of far-reaching bearing, which it seems to us, if completely understood, would undoubtedly greatly elucidate the pathogenesis of asthma

In the normal adult the bone marrow is the chief place of formation of the eosinophil cells (Ehrlich) This conception is substantiated by the frequency with which mitotic cell divisions of these cells are found in this locality Additional evidence is furnished by the increased

number of these cells in the bone marrow in cases of high blood eosinophilia ²⁶

From this viewpoint any increase of the eosinophils in the circulating blood and in the tissues is to be considered as a (protective?) reaction of the leukopoietic centers of the bone marrow to the stimulus of an unknown toxic substance. In bronchial asthma this eosinophilotactic substance is either actually formed in the tissues of the respiratory system or it has, wherever formed in the organism or wherever introduced to it from without, an elective affinity for this system. Such an elective organ localization of chemical substances is not to be considered as a special postulate for this problem but constitutes the basis of most pharmacodynamic actions.

There are, however, many histologists who consider the local eosinophilia in the bronchi as a true primary autochthonous tissue eosinophilia. They believe that the eosinophil cells are formed in the bronchial tissue through myelocytic metaplasia from the perivascular connective tissue cells over the "lymphocyte." The secondary blood eosinophilia may be due, then, to the passage of the eosinophil cells from the bronchial tissues through the bronchial capillaries into the general circulation, or it may be due to a simultaneous stimulation of both the pulmonic perivascular tissues and the bone marrow. The faculty of forming new myelocytic cells in the adult organism we usually concede only to those organs which in the development of the embryo possess the property of leukopoiesis, i. e., the bone marrow, liver, spleen, lymph glands, kidneys and thymus. In certain pathologic conditions (e. g., leukemia), and others associated with severe infections and toxemias (e. g., congenital syphilis) the remnant foci of the embryonic leukopoiesis in these organs are stimulated to proliferation and renewed activity in the direction of their original function. The difficulty that such preexisting myeloid tissue is not known in the bronchial mucosa and submucosa is removed by the assumption that all perivascular adventitial connective tissue is a latent hematopoietic and leukoblastic organ. This conception, based on the early studies of Virchow and later studies of Marchand on the cellular products of inflammation and on the perivascular lymphoma formation of Ribbert, has been especially adopted by Pappenheim, Weidenreich and by G. Schwarz.

As far as the bronchial mucosa in asthma is concerned, the idea of the autochthonous local eosinophilia is mainly based (1) on the occurrence of mononuclear eosinophil cells in the sputum and the bronchial tissue, (2) on the complete absence of such unicellular elements in the circulating blood, and (3) on the enormous number of the eosinophil

²⁶ Opie, E. Cells with Eosinophil Granulations, *Am J M Sc* **127** 217, 477, 988, 1904

cells, polymorphonuclear as well as mononuclear, in the tissue, far too many, as is argued, to have been accumulated from the blood even if it showed a considerable eosinophilia

The last quantitative argument might be first considered. It is well known that a very marked local tissue eosinophilia does frequently exist without eosinophilia of the blood. This is very often to be observed, for instance, in the periphery of malignant tumors, and then—a rarer incidence—in the pleura and exudate of eosinophilic pleuritis. It is just this discrepancy of the normal amount of eosinophils in the blood and of their abundance in the tissue which is taken as one proof for their local genesis. But it could be shown by a simple calculation that in bronchial asthma enough eosinophil cells can be removed from blood with a normal content of these cells to account even for their most extensive accumulation in the respiratory tissue. Thus Heineke and Deutschmann²⁷ observed during an asthmatic attack a decrease of the eosinophilic polymorphonuclear cells in the blood from 2.1 to 0.4 per cent. Calculated for 1 liter of blood, this means that 126,000,000 eosinophil cells have disappeared from the circulation and could have accumulated by chemotactic emigration in the tissues. J. G. Taylor, in his studies in leukemia, has made a similar calculation.²⁸

What now regarding the occurrence of mononuclear eosinophilic cells ("myelocytes") in the tissues of the asthmatic patient?

Our material furnished us an unusual opportunity for studying this special phase of the question. The tissue eosinophilia was very marked in the first case, bacterial asthma (asthmatic bronchitis), in the fourth case, anaphylactic horse serum asthma, and excessively so in the sixth case—food asthma in an infant. The accumulation of eosinophil cells in the wall of and in the tissues about some of the bronchial capillaries is very striking but in the same section of the same bronchus the walls of and the tissues about many capillaries are free of eosinophil cells. Again, the location of the eosinophil cells varied greatly, in Case 6 they were most numerous between the muscle tissue and the cartilages, while in the other cases they were most numerous in the subepithelial layer. In some cases (Cases 1 and 6) the mucous glands contain many of these cells. In the wall of a blood filled bronchial vein (Case 6), which lies between a cartilage plaque and a muscle bundle, there are three migrating eosinophil cells, each of which lies between adjoining endothelial lining cells and partly inside the vessel. Immediately surrounding the vessel there are many polymorphonuclear eosinophil cells and a few small round cells. Many

²⁷ Heineke und Deutschmann. Das Verhalten der weissen Blutzellen während des Asthmaanfalles, München med Wchnschr **53** 797, 1906

²⁸ Taylor, J. G. Studies in Leukemia, Contribution from the William Pepper Laboratory of Clinical Medicine, Philadelphia, 1900

similar pictures are seen on further careful study of these tissues. The sinuses of the bronchial lymph glands (Case 6) contain many polymorphonuclear eosinophil cells but the sinuses of the mesenteric lymph glands contain only an occasional eosinophil cell. The spleen (Cases 4 and 6) shows very many eosinophil cells, almost all of which are polymorphonuclear.

Most of the eosinophil cells are polymorphonuclear cells with usually two or three nuclear fragments. On closer focusing and study, fine chromatin threads can be seen which connect the parts of the nucleus with each other. There are many cells which on first inspection give one the impression of possessing a single nucleus, but most of these, when studied in different planes of depth, with powerful magnification, are seen to have nuclei with two or three fragments. There remain, however, a few eosinophil mononuclear cells, whose nucleus cannot be separated by the eye in such a manner (Plate 3, C). These mononuclear eosinophilic cells are plainly not larger than the polymorphonuclear elements and are of the same type. Their nucleus is small, opaque, more deeply stained than in the polymorphonuclear cells immediately surrounding them, and its chromatin is very homogenous and pyknotic. The protoplasm surrounding this deeply stained nucleus is completely filled with acidophilic granules and no cells were observed where a transformation of granulopoiesis was suggested by a slightly basophilic stained protoplasm containing only a few eosinophilic granules. We could find no cells, however carefully we searched our preparations, which suggested a mixture of basophilic granulations with the eosinophilic as is found frequently in young alpha myelocytes. There was nothing to suggest transitional or intermediate stages between the many "lymphocytes" ("myeloid lymphoidocytes") and acidophilic cells. Nor were we successful in demonstrating any eosinophilic cells which showed evidence of mitotic division. There were no immature embryonic cell forms such as erythroblasts, promyelocytes or meta myelocytes or megakaryocytes. One would expect to find some of these cells if true myeloid metaplasia was taking place.

On the basis of these studies we reach the conclusion that these mononuclear eosinophil cells are not alpha myelocytes but degenerative forms of polymorphonuclear eosinophil cells whose nuclear substance has undergone a regressive metamorphosis. This conclusion became most suggestive when we studied the thymus in Case 6. Here we were able to find many large mononuclear eosinophilic cells with a loose structured, more pale nucleus, encircled by a wide protoplasm containing abundant eosinophilic granulations of varying size, i. e., true eosinophilic myelocytes. The presence of such cells in the thymus, of a

2-year-old child is a normal occurrence²⁹ Autochthonous tissue eosinophilia in the thymus can be accepted as proved, for this organ contains active myeloid tissue and is, therefore, capable of metaplastic activation Mitotic cell divisions, erythroblasts, eosinophilic as well as neutrophilic myelocytes have repeatedly been described in this organ

Whether the mononuclear eosinophilic cells in the bronchial mucosa, as Schwarz³⁰ and also Marchand believe, are derived from the binuclear polymorphonuclear cells through amitotic direct cell division is impossible to decide

Our studies, therefore, contain little evidence which would prompt us to abandon the view that the local tissue eosinophilia in the bronchial structure is due to emigration of alpha granulocytes from the blood in favor of the theory of their autochthonous ontogenesis from the perivascular tissue and transformation of the histogenous lymphocytes The chemotactic toxin, fixed (or formed?) by the tissue of the bronchi, exerts simultaneously a stimulus upon the bone marrow in the direction of increased new formation of eosinophilic cells which through the way of the blood reach the bronchial tissue The question of the nature of this eosinoplastic and eosinotactic toxin is closely allied with the physiologic and pathologic significance of the eosinophilic cells in general Ehrlich³¹ suggested nearly twenty-five years ago that eosinophils seem to appear especially in such places in the organism at which many cells are destroyed, especially cells of epithelial type (e g, in carcinomatous tissue) There can be little doubt that certain relations exist between proteolytic digestive processes in the tissues and organs and the accumulation of alpha cells Eosinophilia appears to be a response, a reaction to a stimulus produced by certain substances derived from the catabolism of proteins It has been shown that the eosinophils increase markedly in the tissues of the intestinal tract during the process of digestion, but disappear completely in animals that have been starved³²

Neusser held that eosinophilia is produced in response to the increased activity of glands supplied by the sympathetic nervous system Eppinger and Falta,³³ and their co-workers, on the other hand, see in

29 Schaffer, J Ueber das Vorkommen von eosinophilen Zellen in der menschlichen Thymus, *Zentralbl f med Wissensch*, 1891, 401-417 Dudgeon, L S A Contribution to the Pathology of the Thymus Gland, *J Pathol & Bacteriol* **10** 173, 1905 Fortescue-Brickdale, T M Observations on the Thymus Gland in Children, *Lancet* **2** 1029, 1905

30 Schwarz, E Die Lehre von der allgemeinen und ortlichen Eosinophilie, Lubarsch und Ostertag *Ergebn d allg Path* **17** 1913

31 Ehrlich, P-Lazarus Die Anaemie, Nothnagel's spec Pathol, Ed 1, 1898, p 113

32 Opie Loc cit

33 Bertelli, Falta and Schwerger *Ztschr f klin Med* **71** 1907 Eppinger, H, and Hess, L Die Vagotonie, Berlin, 1910, p 60

eosinophilia a symptom of increased vagus tonus. They attempted to show that substances like pilocarpin, pituitary extract and nitrites, which increase the tonus of the autonomous nerves, produce an experimental eosinophilia³⁴. Their work, however, could not be corroborated by Schwenker and Schlecht.

The whole problem of blood and tissue eosinophilia, in general, but especially in relation to bronchial asthma, reached an entirely new phase since it has been considered from the point of view of anaphylaxis.

There are some scattered observations in immunologic literature which suggest that blood and serum injections into animals are often followed by a considerable increase in the number of eosinophils in the blood³⁵. But the true connection between eosinophilia and the anaphylactic process was first clearly recognized by Schlecht³⁶. He had observed previously that serum injections were sometimes associated with a marked increase in eosinophilic cells in the blood and he ascribed this phenomenon to the introduction of the foreign protein. Later he and his collaborators,³⁷ found that eosinophilia developed regularly on reinjection of sensitized animals. He examined many proteins and their derivatives in this regard and found egg albumin, serum albumin and globulin, and especially, fibrin, efficacious in producing eosinophilia. Peptone acted less promptly and amino-acids (leucin, alanin, phenylalanin, glycin and asparagin) were without action. Schlecht and Schwenker discovered also the eosinophilic infiltration of the bronchi in the lungs of anaphylactic guinea-pigs and in the perivascular tissue in the edema of the Arthus phenomenon. On the basis of this work, eosinophilia is to be considered as a protective reaction of the organism against certain definite decomposition products of heterogeneous and even homologous proteins. We are in complete agreement with

34 Schwenker, G. and Schlecht, H. Ueber den Einfluss sympathico- und autonomotroper Substanzen auf die eosinophilen Zellen, *Ztschr f klin Med* **76** 77, 1912. Bertelli, Falta and Schwerger. Ueber die Wechselwirkung der Drusen mit innerer Sekretion. *S Mittheilung uber Chemotaxis*, 1910, p. 23.

35 Stschatnvi. Histogenese der eosinophilea Granulationen, *Beitr z path Anat u z allg Path* **38** 456, 1905. Schwarz, E. *Loc cit*,³⁶ p. 431.

36 Schlecht, H. Ueber experimentelle Eosinophile u basophile Leukocytose **27**. *Congr f inn Med*, 1910. Ueber die Einwirkung von Serum-injectionen auf die Eosinophilen, etc., *Deutsch Arch f klin Med* **2** 308, 1910. Ueber experimentelle Eosinophile nach parenteraler Zufuhr artfremden Eiweisses und uber die Beziehungen der Eosinophilie zur Anaphylaxie, *Arch f exper Path* **67** 137, 1912. Ueber lokale Eosinophilie beim anaphylactischen Versuche, *Verhandl Congr f inn Med*, 1912, p. 416. Ueber allgemeine und locale Eosinophilie bei Ueberempfindlichkeit gegen organische Arsenpraeparate, *Munchen med Wchnschr* **60** 800, 1913.

37 Schlecht, H., and Schwenker, G. Ueber lokale Eosinophilie in der Lunge anaphylactischer Meerschweinchen, *Arch f exper Path* **68** 163, 1912. Ueber die Beziehungen der Eosinophilie zur Anaphylaxie, *Deutsch Arch f klin Med* **108** 405, 1912.

this point of view and believe that most clinical eosinophilias have to be considered as the reaction of a person in the state of allergy

Probably the clearest example of protein sensitization in the human is pollen disease³⁸ Morphologic studies of the blood of many patients lead us to the conclusion that blood eosinophilia is a constant symptom during the attack In the months of the year in which the patient is free from hay-fever his eosinophilic cells in the blood are, as a rule, not increased If the eosinophilia persists outside of the six or eight weeks of the hay-fever season and a few weeks following it, the patient is usually the subject of multiple sensitization, i e, he is sensitized to other proteins, e g, horse dander, or he is subject to eczema or urticaria, i e, he is sensitized to certain food proteins In the autumnal type of pollen disease due to the pollen of ragweed, sunflower and other compositae, the eosinophilia begins almost immediately on the day when the catarrhal symptoms begin and increases usually progressively until the third week The asthmatic symptoms, however, usually do not become evident until from twelve to twenty days after the yearly resensitization with pollen has begun

These clinical data are mentioned here in this connection because they show how the human organism acts in regard to the emigration of eosinophilic cells from the bone marrow into the blood on yearly parenteral introduction of a foreign protein The eosinophilia of pollen asthma is a reaction of the organism sensitized to pollen protein For most other types of asthma there exists no difficulty in accepting this point of view, they are cases of special protein sensitization either to food, animal or plant proteins Less evident is the meaning of eosinophilia in the bacterial type of asthma, the eosinophilic bronchitis Here the eosinophilic reaction in its relation to protein katabolism and allergy is not at once entirely evident It is certain that bacterial protein possesses antigenic and anaphylactogenic properties and it would be a simple explanation to assume that the infective organism had sensitized the subject in the same manner as the pollen protein This is a possibility But it should be remembered that at least all acute bacterial infections, with the one exception of scarlet fever, are invariably associated with hypo-eosinophilia which, in the convalescence, is followed by hypereosinophilia Aside from the eosinophilia, the evidence for the assumption that micro-organisms produce asthma through sensitization with their own body substance—the evidence for the existence of a true allergic asthma of bacterial origin—is very meagre Skin sensitization tests with bacterial antigens made according to Woodehouse from stock cultures, as well as autogenous cultures, grown from

38 Koessler, K K The Specific Treatment of Hay-Fever (Pollen Disease), Billings-Forschheimer Therapeutics of internal Diseases 5 671-706, 1914

the bronchial expectoration and including anaerobic as well as aerobic organisms, have proved of very little diagnostic value in our hands. After using them in many hundred instances we have scarcely three or four reactions which we could call positive³⁹. Shall we conclude from this failure of obtaining skin reactions to bacterial antigens that all cases of bacterial asthma are in reality cases of true allergic asthma due to sensitization with an undiscovered protein, which we might discover if we would increase the scope of our tests? It is undoubtedly certain that the group of allergic asthmas will steadily increase with improved methods for the preparation of antigens, with increasing their numbers used in the tests and thus detecting new etiologic factors⁴⁰. Yet on the basis of our clinical observations and studies we are led to believe that there remains still a definite group of cases of asthma, between 25 and 30 per cent of all cases, which are of true bacterial origin. Blood eosinophilia in this group of cases is of exceedingly varying degree, it is sometimes very marked, sometimes slight and may even be absent completely.

The production of an eosinophilia through stimulation of the leukopoietic organs is not restricted to intact proteins of antigenic properties. Lower decomposition products of proteins, as albumoses and peptones, too, have the faculty of producing eosinophilia as well as bronchiolar spasm and arterial hypotonus with capillary stasis, the three cardinal symptoms which constitute the syndrome "asthma."

Bacterial asthma may thus be considered as being due to the products which micro-organisms form by their action on the proteins of the body's own tissues or on the proteins of the food in the intestinal tract. It is a peptone intoxication or amine intoxication (aminosis).

Other peptones and amines, while possessing bronchospastic activity, do not exert any eosinotactic stimulus upon the blood forming organs. The study of the formation of these toxic products (amines) by micro-organisms has been the subject of our investigations for many years. Our evidence for the relation of amines to asthma is, while not conclusive, very suggestive, and will form the subject of a special report. Here, we wish merely to point out that the production of amines of bronchospastic and hypotonic action, of which histamin is the chief representative, is mainly dependent on a particular type of otherwise common species of micro-organisms. Thus, of twenty-nine strains of *B. coli* studied, six were able to form histamin on a synthetic medium and no other chemical reaction, as fermentation of sugars, etc., could be

39 A detailed account of the clinical phases of our work will be published in the near future.

40 Cooke, R. A. New Biologic Factors in Bronchial Asthma. *J. Immunol.* 7: 147, 1922.

found which would set this group of colon bacilli aside, except their faculty of decarboxylating amino-acids with the formation of amines⁴¹

From our viewpoint, then, eosinophilia, if present, is a very important symptom of bronchial asthma. It is evidence of (1) the allergic type of asthma due to sensitization with proteins of antigenic character, or (2) of an intoxication with higher peptones. If constantly absent it forms, together with other clinical symptoms, strong evidence that the asthma is due to an intoxication with lower peptones or with amines or that the bronchospasm is produced by extraneous factors, pressure on the vagus by tumors or aneurysm (symptomatic asthma)

ABSORPTION ATELECTASIS IN BRONCHIAL ASTHMA

If the passage of gases (air) through a bronchiole or small bronchus is interrupted for some time, either through bronchiolar spasm or through obturation with secreted mucus, the air contained in the alveoli connected with that occluded tube is gradually absorbed by the blood of the pulmonary capillaries and an area of atelectasis is formed. In two of our cases, the infant with food asthma (Case 6) and the adult male (Case 4), who succumbed to an injection of horse-serum, definite areas of this character were shown. In the infant there are two distinct groups of areas scattered rather diffusely and which may be interpreted as representing two stages in the production of areas of absorption atelectasis. In one group of areas, apparently the newer stage, there is an obliteration of the alveoli by an exudate containing only a few cells, chiefly polymorphonuclear neutrophils. In these areas the bronchioles are completely occluded by a mucous exudate. In the other group of areas, apparently the later stage, there is such a complete obliteration of alveoli, that all vestiges of lung structure, except contracted bronchioles, are absent. Both of these areas are sharply defined and are separated from normal appearing alveoli only by the normal amount of fibrous tissue which separates the units of lung tissue in the child. We can think of these areas as representing two distinct end-results of different asthmatic attacks. In one, the newer, the occlusion of a small bronchus cut off temporarily that portion of the lung which connects with it and the exudation resulted, in the other, the older stage, the occlusion of a bronchus or bronchiole, occurred in a previous attack and lasted long enough so that complete organization of the lung connected with it resulted. In the adult (Case 4) we find also areas of lung tissue in which there is complete obliteration of all alveoli. In these areas, which are less sharply defined than in the infant's lung, there is a larger amount of fibrous tissue which surrounds, zonelike, all blood vessels

⁴¹ Hanke, M. T., and Koessler, K. K. Studies on Proteinogenous Amines, XII, *J. Biol. Chem.* **50** 131, 1922

and small contracted bronchioles. These areas we interpret as representing old lesions following previous asthmatic attacks. No other lungs, whether normal, asthmatic or nonasthmatic, showed such areas. The presence of absorption atelectasis has heretofore not been observed in bronchial asthma. Pathogenetically it is, like the acute emphysema, the result of the bronchiolar obstruction and represents the ultimate stage of the emphysema in an area of lung tissue in which the normal gaseous exchange through the bronchi has become completely interrupted.

Some authors⁴² have attempted to set apart certain forms of paroxysmal dyspnea in children as a new morbid entity, which they call "bronchotetany." This, according to its originator (Lederer), is a symptom complex fundamentally distinct from bronchial asthma, though also due to bronchiolar spasm. The distinction is based first on the clinical observation that bronchotetany is found usually only in children who show some definite symptoms of spasmophilia, such as laryngeal spasm, carpopedal spasms or eclampsia, and second, on the evidence of the pathologic anatomy that all fatal cases of bronchotetany are associated with the formation of areas of atelectasis. For after studying the published reports of twelve postmortem examinations of bronchial asthma, all of which we have cited in our historical review, this investigator reaches the conclusion that "intense bronchospasm leads in asthma only to emphysema, never to the formation of atelectasis, in bronchotetany always to atelectasis." From the clinical description it is not clear to us how the cases cited as bronchotetany differ from true (allergic?) asthma in children. The presence of definite areas of absorption atelectasis in our two cases of bronchial asthma, shows that also the specific pathologic criteria evoked for the existence of this new entity, bronchotetany, do not hold true.

SUMMARY

The pathologic histologic examination of the finer structure of the bronchi and their branches in our six cases of bronchial asthma suggests a certain parallelism between the clinical picture and the structural changes. Of those cases developing seemingly on a bacterial basis, one was during life a well defined exudative type (Case 1), characterized by an abundant secretion (bronchorrhea) which was one of the chief clinical symptoms associated with the paroxysmal attacks. The anatomic parallel of this picture is furnished by the striking hypertrophy of the mucous gland system of the bronchi.

⁴² Lederer, R. Ueber Bronchotetanie, *Ztschr f Kinderh* **7** 1, 1913, and *ibid* **23** 79, 1919. Chronische Bronchitis, Bronchial Asthma und Bronchotetanie, *Ergebn d inn Med u Kinderh* **19** 564, 1921. Rietschel, H. Bronchotetanie, Bronchialasthma und Asthmatische Bronchitis, *Monatschr f Kinderh* **12** 261, 1913.

One other case of bacterial asthma (Case 2) was characterized clinically by a more or less unproductive cough which led to the attacks of bronchospasm. The chief pathologic changes seen in this case are the hypertrophy of the smooth muscle system and the atrophy of the mucous glands.

The two cases of food asthma (Cases 3 and 6) are characterized pathologically by hypertrophy of both glandular and muscular systems, both of which undoubtedly played a rôle in the production of the stenosis.

One case of true allergic asthma (Case 4) in a person hypersensitive to horse serum, calls to mind the picture seen in the lungs of the guinea-pig in the classical anaphylactic experiment, i. e., the acute emphysema and the marked contraction of the bronchi and bronchioli by the well developed muscle layer. The irregular thickening of the walls of the bronchial arteries recalls the nodal arrangement of these arteries described by Schultz as occurring in the guinea-pig.

The outstanding finding in our study is the evidence that the actual thickness of the walls of bronchi and of bronchioli of more than 0.2 mm outside diameter is increased, as compared with similar structures in nonasthmatic persons. This difference is due to increased thickness of all layers from the epithelium to the outer fibrocartilaginous layer. Hyperemia and cellular infiltration of the wall and increased activity of the glands lead to swelling and thickening and this can produce, mechanically as well as chemically, irritation of the peripheral nerve endings in the tube, which may indirectly cause bronchospasm. The abundant secretion of the epithelium and the hyperactive glands obstruct, in some instances completely, the already narrowed lumen of the middle-sized and small bronchi and the bronchioli. In this way both systems, the exudative and the bronchomuscular, act simultaneously in the production of the stenosis, in some cases one more than the other but always both to some extent. Even in the purely allergic asthma of the infant 16 months old, which at that age already showed definite thickening of the bronchial wall as compared with an infant of the same age, the exudation into the bronchi and bronchioli with complete obstruction of some is proof of this combined involvement. These observations make it plain that in man, at least, the allergic reaction of the tissues is not confined alone to the smooth muscle fiber system, but involves also the whole organ system which serves exudative processes, endothelium, epithelium, capillaries and glands.

The increased thickness of the wall, the hyperactivity of the glandular system, the bronchoconstriction, as well as the emphysema, are not present to the same degree in all parts of the lungs but often involve one lobe or part of a lobe to a greater degree than others.

The anatomic substrate of the bronchospasm is mainly furnished by the hypertrophy of the smooth muscle fiber system. The evidence of a narrowed lumen and the folding of the epithelium while present has to be interpreted with great care.

The chief cellular symptom of the allergic reaction in man is the eosinophilia. In only one disease, bronchial asthma, does a blood, sputum and tissue eosinophilia occur simultaneously. The eosinophilic infiltration of the bronchial wall in asthma is a characteristic histologic criterion of bronchial asthma, but if absent it does not exclude asthma. Since eosinophilia is regarded as one of the chief clinical and pathologic symptoms of allergy, its constant absence in certain forms of bacterial asthma is regarded as one important part of evidence that there are types of asthma which may not be of allergic origin. This form may be regarded as due to an intoxication with peptones or amines, broncho-spastic poisons, which are formed by the action of micro-organisms on tissues.

This work would not have been possible without the kind interest and aid of several colleagues. To all of them we wish to express our grateful appreciation. Especial thanks are due to Drs H G Wells, T H Boughton, B O Raulston, W White, F H Stangl, W G Hibbs and C J Eldridge for assistance in obtaining some of the normal and pathological material used in this study and also to Mr K Toda for his excellent colored drawings.

THE INTESTINAL DIGESTION OF CONNECTIVE TISSUE

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Adolph Schmidt¹ has persistently claimed that connective tissue is digested only, if at all, in the stomach, and never in the small intestine. This view has been accepted by such investigators as Sahl² and Strasburger³ abroad, and in this country among others by Dr Charles D Aaron⁴.

As a corollary to this statement, it follows, as emphasized by Schmidt, that the finding of large amounts of undigested connective tissue in the stool, particularly after the administration of his test diet, is an indication of a disturbed gastrogenic function, since there is no participation of the small intestine in the digestion of connective tissue.

Assuming the claim to be correct, this phenomenon has both a theoretical and practical significance. Theoretically, this is important in indicating that from the standpoint of the digestion of one substance at least, the stomach was absolutely essential, and no vicarious functioning on the part of the small intestine was possible. From a practical standpoint, the claim was of value, in that through a careful examination of the stool, a gastrogenic disturbance could be predicated, from the finding of large amounts of undigested connective tissue.

I attempted to determine the truth of the matter from a study of the digestion of connective tissue when introduced directly within the small intestine of the human being.

Observations on the behavior of intestinal fluid, from a digestive standpoint, when present in a test tube, are open to the following objections:

First—Once the intestinal fluid is placed in a test tube, the environment is definitely altered. In this way, the behavior of the fluid where any substance is introduced within it, may not necessarily indicate the manner in which the fluid behaves when present in its normal environment within the small intestine.

1 Schmidt, A. The Test Diet in Intestinal Diseases, Philadelphia, F. A. Davis & Co. Translated by Dr Charles D. Aaron, 1909.

2 Sahl, H. Diagnostic Methods of Examination, English translation, edited by N. B. Potter, Philadelphia, W. B. Saunders Company, 1911, p. 433.

3 Strasburger, J. Examination of the Feces, Diseases of the Digestive System, edited by Frank Billings, New York, D. Appleton & Co., 1906, p. 605.

4 Aaron, C. D. Diseases of the Digestive Organs, Philadelphia, Lea & Febiger, 1921.

Secondly—The specimen within the test tube represents the character of the intestinal fluid at the time it was withdrawn, but does not necessarily indicate the nature of the intestinal fluid at some other time. This is supported by the fact that fluid removed by the fractional method from the small intestine through the intestinal tube shows definite variations in the strength of the pancreatic ferments in the separate specimens. Thus, the digestive efficacy of any specimen of fluid within a test tube is not an absolute criterion as to the power of the fluid within the small intestine, where there is a constant variation in its enzymotic content.

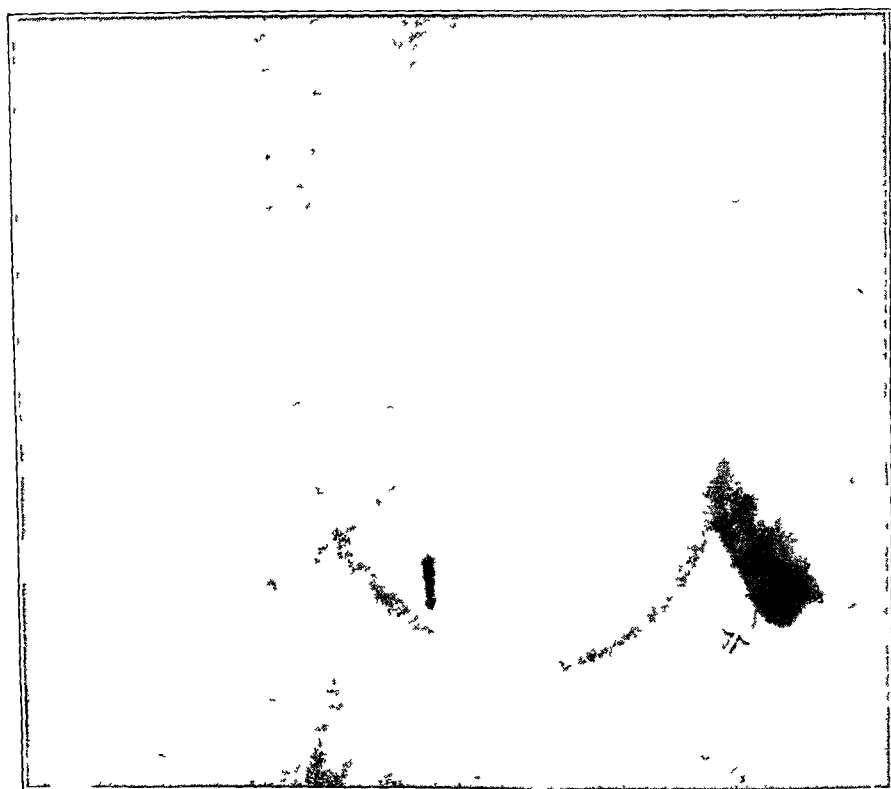


Fig 1—Roentgenogram of tube shortly after entering the small intestine. The arrow points to the metal tip which has been sewed on to the end of the rubber tube with kangaroo tendon.

Third—A process of stagnation occurs under such conditions which is absent in the small intestine, where there is a constant flow of freshly secreted fluid.

For these reasons, conclusions based on the behavior of intestinal fluid within a test tube must be made with caution, since the conditions are not entirely similar to those within the small intestine itself.

It is possible to study the digestive effect of intestinal fluid on connective tissue introduced directly within the small intestine. This

can be done in the manner I described in a previous communication⁵ A special intestinal tube is used to the end of which the metal bulb might be sewed on with either silk or chromicized catgut By sewing the bulb on with silk, it became permanently attached By employing chromicized catgut as a suture material, the bulb after reaching the intestine became detached through the digestion of the catgut I employed this principle, substituting medium kangaroo tendon in the

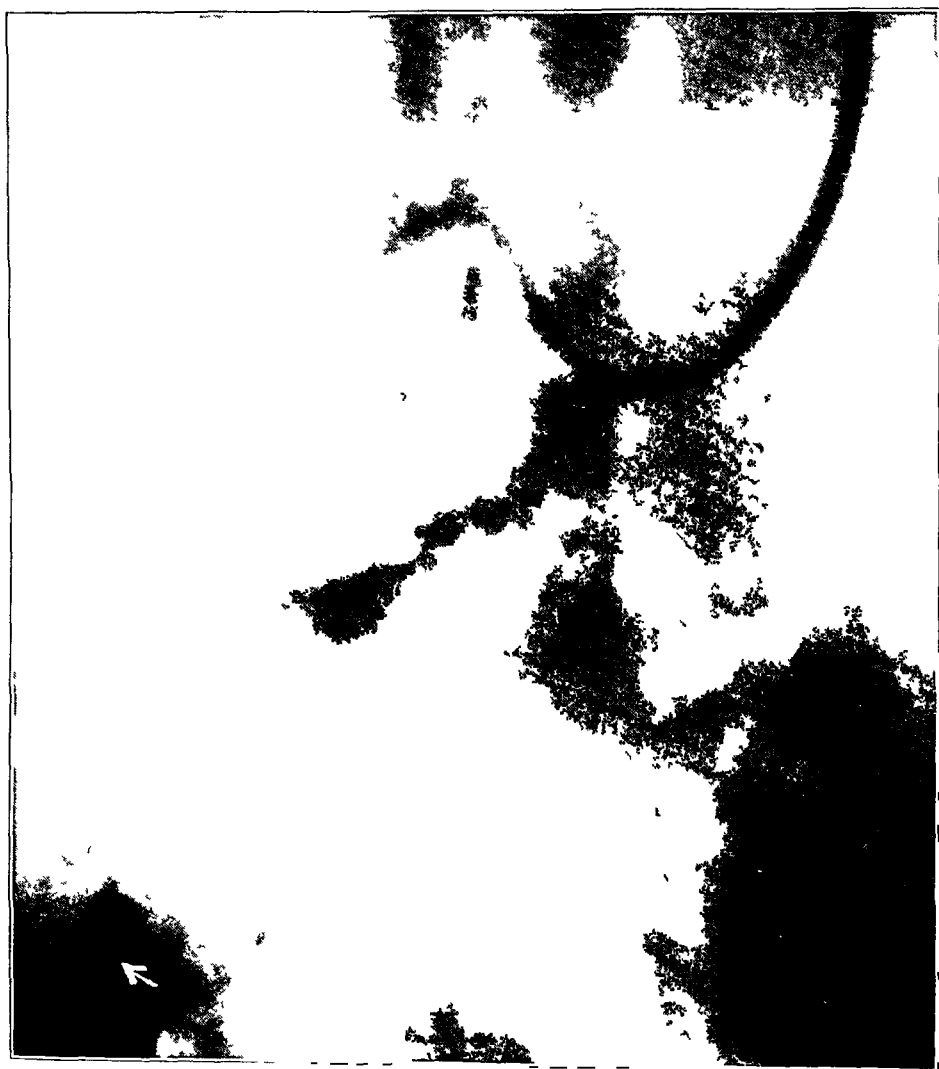


Fig 2—Roentgenogram of tube taken twenty-four hours later The arrow points to the metal tip which has become detached from the end of the rubber tube, indicating that the kangaroo tendon has become digested

place of catgut as a material with which to sew the metal tip to the end of the rubber tube The tube was then passed into the small intestine, as indicated in Figure 1 Roentgenograms were taken at varying intervals At the end of twenty-four hours, a roentgenogram (Fig 2) indicated that the bulb had become detached The con-

⁵ Buckstem, J The Intestinal Tube, J A M A **74** 664 (March 6) 1920

clusion appeared justified that the release of the bulb from the end of the tube had occurred as a result of the digestion within the small intestine of the connective tissue suture in the form of kangaroo tendon

There was, however, one definite objection to this procedure. Gastric analysis in this case indicated that the acid values were within normal limits, and that pepsin and rennin were present. It was, therefore, impossible to determine how much of the digestion had

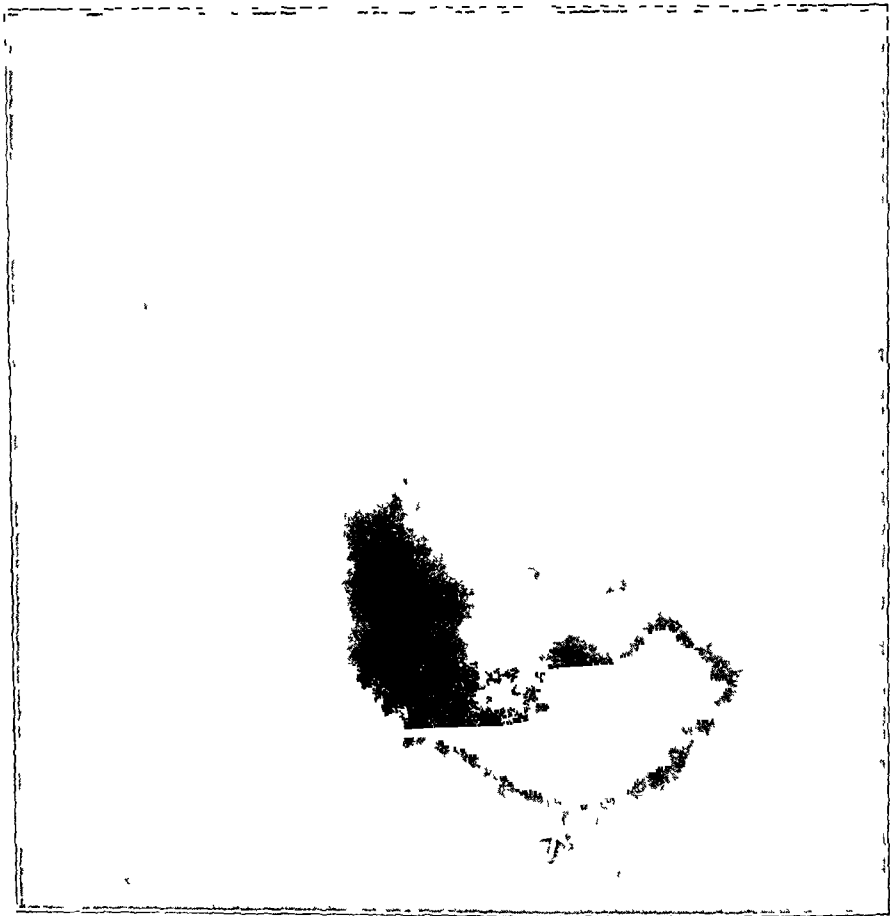


Fig 3—Roentgenogram of tube after reaching the small intestine in a patient with achylia gastrica. The arrow points to the metal tip which has been sewed on with kangaroo tendon.

actually occurred while the tube was still present within the stomach and before the end had reached the small intestine. It was conceivable that the digestion had actually occurred within the stomach, that the metal tip cohered to the end of the rubber tube, and was detached by some sudden exertion on the part of the patient, or as the result of forcing the tip free, in injecting the rubber tube with barium by means of a syringe in taking a roentgenogram of the tube.

This preliminary gastric digestion was to be considered, particularly since a small strip of the tendon, when placed in the gastric secretion of this patient, became completely digested within twenty hours

Therefore, I endeavored to ascertain the digestibility of the tendon within the small intestine of a patient with achylia gastrica. The absence of acid secretion and of enzymes in the gastric contents was determined by the fractional method of examination, and verified on three different occasions. Moreover, in this case, the rubber tube with the tip sewed on with kangaroo tendon, was permitted to remain



Fig 4—Roentgenogram of tube taken forty-eight hours later. The arrow points to the metal tip which has become detached from the end of the rubber tube. This indicates that the kangaroo tendon has become digested although an achylia gastrica was present.

in the gastric contents for thirty days, with no liberation of the bulb and no digestion of the suture material. Nevertheless, although the effect of gastric digestion on the tendon could be excluded while the tube was passing from the stomach into the small intestine, roentgenograms indicated the release of the bulb from the end of the tube within forty-eight hours after the intestine had been reached (Figs. 3 and 4). On removing the tube, no evidence of the tendon could be found. It is an interesting fact that fluid removed from the small

intestine of this patient showed the presence of all three pancreatic ferments, although the fluid was removed in the fasting state, in the absence of free hydrochloric acid, and with the exclusion, as nearly as possible, of any psychic stimulation

In 1890, Von Noorden⁶ claimed that even when gastric secretion was no longer present, the digestion of food could, nevertheless, proceed in a normal manner. From the evidence presented above, it is evident that connective tissue digestion forms no exception to this statement, and that the small intestine may be completely vicarious in its digestive function

CONCLUSION

1 A method is presented for the study of the digestion of connective tissue, when introduced directly within the lumen of the small intestine of the human being

2 Connective tissue digestion may occur within the small intestine, and is not dependent entirely on gastrogenic function

3 The absence or presence of connective tissue in the stool, throws no light on the nature of the gastrogenic function, since the small intestine is definitely involved in its digestion

⁶ Von Noorden, C. Ueber die Ausnutzung der Nahrung bei Magenkranken, *Ztschr f klin Med* **17** 137 1890

PSYCHOLOGIC TESTS APPLIED TO DIABETIC PATIENTS ¹

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Diabetes is well known to exert an important influence on the central nervous system. Kiaus¹ recently summarized the more common neurologic lesions, and the psychoses occasionally associated with diabetes have been the subject of numerous studies.

The diabetic patient, on his own part, complains of loss of memory and of poor ability to concentrate the attention. So far as we are aware, there are no objective data which either substantiate or contradict this clinical picture in reference to attention and memory. We have undertaken to gain some light as to the extent of the impairment if such exists, comparing diabetic patients as a group with controls who are of about the same mental status.

METHOD

At the New England Deaconess Hospital in Boston, Dr. E. P. Joslin has for some years conducted twice a week a patients' class in diabetic hygiene. We took advantage of meetings of this class which commonly contained all of the ambulant diabetic patients then in the hospital together with a few who had returned for observation, and conducted group tests over a period of two and one-half months. Usually from eight to fifteen persons were present. Data were collected on forty different diabetic patients. Some were tested several times, others only once, the group consisted of seventeen men and twenty-three women, ranging in age from 15 to 55 years, with an average of 46. At the time patients were first tested they were without exception free from acidosis but usually not sugar free. None were tested on a fasting day or on a day just succeeding a fast. Most of them were in the hospital for the first time and their initial tests were usually within a week of admission.

The control group consisted of two doctors, nurses and mostly of relatives and friends of patients. It is, of course, difficult to secure a control group which can be proven comparable to the diabetic group in everything except the diabetes. We took for controls adults who visited the class and were not patients. Several of the patients in the diabetic group were people of superior intelligence and of good education who probably in regular mental tests would have ranked above many of

* From the Nutrition Laboratory of the Carnegie Institution of Washington, and the New England Deaconess Hospital, both in Boston.

¹ Kiaus. *M. Clinics N. America*, July, 1920, p. 225.

those in the control group The possibility of making a mental test of each diabetic was considered, but it seemed unwise to add anything more to their burden

The four simple group tests which we used required about twenty-five minutes They were conducted in a large, light room, comparatively free from distraction and following breakfast when the patients were usually at their best The tests were as follows

1 *Cancellation of Digits*—This is one of the Woodworth and Wells² tests in which one thousand digits, each appearing an equal number of times, are printed in twenty lines of fifty digits each The subjects methodically crossed out a certain digit every time it appeared, completing as much of the blank as possible within a time limit of two minutes

2 *Memory Span for Digits*³—A series of numbers were pronounced slowly and regularly, and at the end subjects tried to write them down in proper order Trials were given, starting with five place numbers and gradually working up to nine place numbers The same amount of material was given at each test and subjects were marked on the per cent of the total material correctly reproduced

3 *Memory Span for Four-Letter Words*⁴—A list of twenty-five one syllable English words, each word composed of four letters, was read at the rate of one word per second When the list had been completely pronounced to the patients, they then wrote down all of the words that could be recalled without regard to order

4 *Addition of One-Place Numbers*⁵—These addition blanks were very legible, being printed in 12 point type, well spaced, arranged in blocks of 100, i e, ten digits in a column and ten columns wide The patients added as many columns as possible in five minutes

The tests on the different days were, so far as we know, of equivalent difficulty and were always conducted in the same manner Due to the readiness with which diabetics are fatigued, it was not possible to make tests as long or as intensive as otherwise would have been desirable So far as possible, we tried to make the testing period pleasurable rather than boresome, and if patients showed disinclination to do them, they were freely excused without argument on our part A careful but unobtrusive watch was kept as to the accuracy with which instructions were followed and doubtful records were thrown out

2 Woodworth and Wells Psychol Mon **13** 24, 1911

3 Whipple Manual of Mental and Physical Tests, Baltimore, 1915, Pt 2, p 155

4 Benedict, Miles, Roth and Smith Human Vitality and Efficiency Under Prolonged Restricted Diet Carnegie Inst Wash Pub 280, 1919, p 142

5 Ibid p 143

RESULTS OF INITIAL GROUP TESTS

In the first place, we will compare the ability of diabetics beginning treatment with other individuals equally unfamiliar with the tests

Cancellation of Digits—Per cent of task performed

39 diabetics Range, 19-75, average, 48, variation, 23%, errors, 35%
15 controls Range, 37-100, average, 61, variation, 21%, errors, 31%

The diabetics were able to accomplish an average of 48 per cent of the task while the controls covered 61 per cent in the same time. Substantially the same result is shown in the ranges covered by the subjects of the two groups. The per cent variation (coefficient of variability) among the diabetics is only a trifle higher than among the controls, and the same applies to the per cent of errors which is small in both. The difference lies, therefore, in the amount accomplished rather than in the degree of accuracy, the diabetic patients showing an inferiority of about 21 per cent if we reckon the controls as 100.

Objection may be raised that visual defects so common in diabetes account for this difference. In that case, we should expect a higher percentage of error among the diabetics whereas the percentages are almost the same. Furthermore, the patients were specifically questioned with regard to this point, and two patients were excluded who were at the time experiencing the well known temporary blurring of vision. Ophthalmoscopic examination in several showed no retinal lesions. It seems from this that the diabetic is retarded, but whether this is in discrimination or in speed of movement or both cannot be determined from this test.

As the test of memory span for digits was necessarily brief, it was not possible to give enough trials with six place, seven place, etc. numbers to certainly establish the number of digits which could be recalled correctly.

Memory Span for Digits—Per cent of material recalled

39 diabetics Range, 30-81, average, 56, variation, 20%
14 controls Range, 40-100, average, 66, variation, 21%

If all of the material given in this test be considered, then the diabetics, on an average, recalled 56 and the controls 66 per cent of it. This difference is reflected in the ranges covered by the individuals composing the two groups. The per cent of variation within both groups is nearly the same. The diabetics showed a decrement in this memory span test of 15 per cent. As an approximation we might say that if the average control is able to remember for immediate recall a seven-place number, the diabetic can barely remember one of six places, and, as compared with normals, they are much more likely to find difficulty with even a four-place telephone number.

In the memory span for words, the diabetics showed a larger variation among themselves from their average number of words correctly recalled than did the other groups. One diabetic could not correctly recall any word (two words were put down but they were both errors, i.e., not pronounced in the list) and another patient, a school teacher, had eleven words correct and one error word.

Memory Span for Four-Letter Words —

39 diabetics	Range, 0-11, av correct, 4.9, variation, 31%, av errors, 1.7
18 controls	Range, 3-10, av correct, 6.2, variation, 24%, av errors, 1.9
24 students	Range, 3-13, av correct, 7.0, variation, 24%, av errors, 1.4

On the average, the diabetic patients show 4.9 correct words as compared with 6.2 for the controls and 7.0 for a group of male college students who were given the same test in another experiment at an earlier time. It is common in such a test that some words are written down which were not in the list pronounced for memory and which have not been obviously suggested on the basis of similarity of sound. Such may be called errors. Of the thirty-nine diabetics, thirty-one gave such errors which range from 1 to 4 and average 1.7. The controls and students show average errors of 1.9 and 1.4 per cent, respectively, so there seems no significant difference between the diabetics and the other groups as to number of wrong words entered. An illustration of the difficulty which diabetics experience in remembering instructions came out in this test. The word "go" was written down by four of the diabetics in spite of the instruction "all the words are four-letter words. When I have finished pronouncing the list, I will say the word 'go' which is a signal for you to start writing." On the basis of the number of words correctly recalled in this test, the diabetics show a decrement of 21 per cent below the controls who themselves are 11 per cent poorer than the group of college students.

Probably of the group tests given, addition is most likely to have been practiced through the regular occupations of certain subjects. It is difficult to secure groups of people who are directly comparable in respect to this factor of preliminary practice. Any person who without recent practice can correctly add thirty columns of ten digits each within five minutes may arbitrarily be considered as being professionally practiced in addition. To simplify comparison we have excluded each such case among the diabetics, controls and students compared. As stated, many of the patients were very intelligent and capable people. It is significant to find that among thirty-seven diabetics who took the addition tests, seven at the first trial correctly added thirty or more columns. In each case the person is known to be an accountant, a school teacher,

or store keeper Besides these, there was one accountant and one teacher whose scores we have not omitted who each did twenty-eight columns correctly It is, perhaps, questionable that these should have been allowed to remain in the group Of the eighteen controls, only one, a doctor, did as well as thirty columns, and of the twenty-four college students who took the test, three did at the rate of thirty or more columns in five minutes One of these students was a bank cashier On this basis the comparative results are as shown in Table 1

TABLE 1—ADDITION OF ONE-PLACE NUMBERS

Subjects	Columns Correctly Added	No Incorrect
30 diabetics	Range 2-28, average 14 0	3 0
17 controls	Range 4-24, average 14 7	2 9
21 students	Range 5-28, average 16 9	4 6

If we consider the average number of columns correctly added, the thirty diabetics did only 5 per cent less than the seventeen controls, while the latter were 13 per cent poorer than the twenty-one college students Since in addition accuracy is of prime importance rather than the number of columns attempted, we may deduct the average number of columns incorrectly added from the correct for a combined score. In this way we find

Diabetics, 11 0

Controls, 11 8

Students, 12 3

Taking the controls as a basis, the students are 4 per cent better and the diabetics 7 per cent poorer

In this discussion of addition we have eliminated the professionally practiced adders for reasons which seem pertinent The diabetics do not show a large decrement in their ability to add, and it may fairly be questioned if the decrement found is a real fact Two or three very poor adders might press the average below that found for normal controls As we have eliminated the very expert, we may do likewise for the extremely inefficient and thus compare in all cases modal groups Any person who in five minutes cannot add correctly more than five columns of ten digits each we will arbitrarily exclude This eliminates three of the thirty diabetics, two of the seventeen controls, and one of the twenty-one students, and provides for number of columns correctly added the following scores

Diabetics, 15 3

Controls, 16 1

Students, 17 5

Viewed in this way, the diabetics are again 5 per cent poorer than the controls who, in turn, are 8 per cent below the students It is a treacherous thing to draw conclusions from arbitrarily selected data,

but from that available, viewed from different angles, it appears that the diabetic patients suffer a small decrease of about 5 per cent in their ability to do simple sums in addition ⁷

REPEATED GROUP TESTS ON DIABETICS

We have discussed what the diabetic patient at the very beginning of treatment can do in his first performance of certain psychological tests given under practically ideal group conditions. As compared with available controls, we have found that his performance level is somewhat poorer, in amount, 5 to 20 per cent. It is quite important to discover if his ability to improve with practice is very different than normal. There were twenty diabetics who took the tests two or more times. A comparison may be made of their first and second trials to note if the latter averages are the higher, and if so, how much in terms of per cent of the first trial averages. Such a comparison among twenty diabetic patients, seven controls and eleven young men college students is embodied in Table 2.

TABLE 2—THE AMOUNT OF IMPROVEMENT BETWEEN THE FIRST AND SECOND TRIALS WITH PSYCHOLOGIC TESTS

Subjects	Trials	Cancellation	Memory Words	Memory Digits	Addition	Average
20 diabetics	First	48	47	55	20.6	
	Second	56	57	68	21.9	
Per Cent improvement		17	21	23	6	17
7 controls	First	66	59	58	19.3	
	Second	71	66	63	22.1	
Per Cent improvement		8	12	9	14	11
11 students	First		73		19.6	
	Second		87		21.0	
Per Cent improvement			19		7	13

Without specifically discussing the average scores made in the different tests by the different groups of subjects we may note the per cent of improvement with practice. In this, the diabetics show percentages of gain as follows: cancellation, 17, remembered words, 21, remembered digits, 23, and columns correctly added, 6. All four tests gave an average gain from practice of 17 per cent. The seven control subjects who took the tests twice show gains of 8, 12, 9 and 14 per cent, with an average of 11 per cent. The eleven college students who, under normal conditions but with a somewhat longer interval between trials, took the memory for words test and the addition test a second time, demonstrate improvement of 19 and 7 per cent, respectively. In the

⁷ The question may be raised as to any change in the accuracy of addition work by the seven diabetics who were discarded as being expert. These averaged 37.7 correct and 2.5 columns incorrect. The three students who were discarded averaged 37.8 columns correct and 3.0 incorrect. While the one discarded control showed 33 and 1 columns

addition test, the controls gained more than did the diabetics but in the three other tests the diabetics are well in the lead with large percentages of improvement

It must be recognized that in the trials which came after the first experience with the tests, the subjects were often sugar free and were receiving more food. This doubtless contributed to their comfort and efficiency. We have no diabetic quotient, i.e., no way of numerically stating the diabetic condition of a patient or of a group of patients. Such a quotient would be useful in assessing the value and progress made with different types of treatment and for correlation of diabetes status with numerous other factors and conditions. At present, it is impossible to say to what extent the improvement shown is due to improved physical condition or to the subsidence of certain symptoms. Of twelve patients who were tested from three to nine times we found that the improvement in the performance of these tests shown at the second trial was maintained with a slight tendency to a continued gain in efficiency. We may at least say that the treated diabetic quickly responds in psychologic level and is able to learn rapidly from practice, as is shown in repeated tests. It is also clear that under treatment he rather quickly approaches the normal, although he seemingly does not reach that level. This rapid response to adequate treatment is a fact which should much encourage both physician and patient.

PSYCHOMOTOR TESTS OF INDIVIDUAL DIABETICS

A few diabetic patients were given certain neuromuscular tests at the Nutrition Laboratory. These measurements were made with a view to sampling the performance of these subjects as to their quickness of action, accuracy and steadiness of muscular control, etc. Data may be reported for five persons, two women and three men, all of them very intelligent and cooperative subjects. All were subjects of pronounced diabetes and had been under treatment for some time, all were free from sugar and acidosis when tested, but their total food intakes were low, and, as a class, they were quite emaciated. The testing was done in the morning shortly following breakfast and required about two hours. Only one subject came on any day. Care was taken to instruct and adjust each patient to the tests. Rest periods were introduced so that fatigue might be slight.

Detailed descriptions of the tests and methods used have been published elsewhere. It will be sufficient here to characterize them briefly.

1 Station. Standing erect for two minutes with the least possible swaying at the vertex, eyes closed, feet in V position.⁸

⁸ Miles. Static Equilibrium as a Useful Test of Motor Control, *J. Indust. Hyg.* 3: 316, 1922, p. 186.

2 Finger movement Alternate flexion and extension of a finger at maximum speed for ten seconds⁹

3 Eye movement Speed in looking successively back and forth from one mark to another while the eye is being photographed¹⁰

4 Eye reactions Quickness of turning the eye to a new point of regard as to a flash sign that unexpectedly illuminates¹¹

5 Pursuit coordination Catching in a narrow cup liquid that is expelled from a swinging pendulum¹¹

The results in these five tests are briefly presented in the same order as above

1 A group of twenty-seven normal adults, sixteen men and eleven women, of widely varying ages, weights and statures, gave an average of 740 mm in the station test This value represents the sum for all the swaying movements, front, back, left and right, during a period of two minutes standing with eyes closed and feet in V position Every diabetic tested swayed more than 740 mm while no normal adult did as poorly as the average for the five diabetics which was 1160 mm Accordingly, they show about 50 per cent increase in swaying

2 In this modified and graphic form of the tapping test, thirty normal men were able, on the average, to execute 66.5 finger movements in ten seconds With the same apparatus and conditions the five diabetics average 54.5 movements, i.e., they were 18 per cent slower The difference in level between the two groups is also indicated in that no diabetic was as fast as the average for the normals, and only one man in thirty was as slow as the average for the diabetics

3 The speed with which the eye can move horizontally back and forth between two marks which are located 40 degrees apart on the arc of vision has been found a sensitive measure in other studies Averaging together movements from left to right with those from right to left we find that the five diabetics show a group average of 0.102 seconds for an eye movement of 40 degrees In comparison with this, twelve normal men¹² at their initial trial of this test show an average eye movement time of 0.092 seconds, by which it appears that the diabetics are about 11 per cent slower Both groups took the test in the morning when they were quite free from any sleepiness

4 The eye quickly turns in the direction of any part of the visual field that suddenly moves or changes, and the every day experiences of life cause this act to be rather well practiced In the eye reaction test, the subject looked at the center of a dark screen which was pierced with many small holes, through any one of which a light could be made

9 Ibid p 184

10 Ibid p 159

11 Miles A Pursuit Pendulum, *Psychol Rev* 27 361, 1920

12 Ibid p 619

appear suddenly The photographic record showed the elapsed time from the moment the light was turned on until the subject's eye began to turn toward it Quite a number of trials were invariably made on each person tested Twelve normal men gave an average eye reaction time of 0.237 seconds while the five diabetics show 0.254 seconds, which is thus slower by only 7 per cent

5 It requires rapid and accurate coordination of eye and hand to catch liquid expelled in a stream of one-eighth inch diameter from the tip of a pendulum which swings through a horizontal distance of 70 cm in 1 second, the mouth of the cup being six-eighths of an inch in diameter But everyone, even small children, can do something at the test A single trial in this case consisted in catching the liquid expelled during one double swing of the pendulum and the whole test comprised twenty-five such trials A group of fifteen men and ten women at their first performance caught a total average of 378 c c out of a possible 1250 c c As against this, our five diabetics averaged 291 c c, which is poorer by 23 per cent So far as is known, the diabetics were not at any disadvantage in the tests which were made at the Nutrition Laboratory In all of the tests, they seemed to do definitely poorer than the so-called "normal" subjects who we felt could reasonably be compared with them The five diabetics who were tested were all persons whom we selected with the impression that they would do as well, or, perhaps, better than the average on account of good intelligence, education and adaptability It is altogether probable that another group of five would show somewhat different results Knowing the subjects thoroughly, we feel that results obtained in our tests are probably characteristic, although on the actual amount of change we cannot, of course, be dogmatic

To what extent the carefully treated, severe diabetic gradually changes from year to year is at present only a matter of surmise After making the tests just described, we had an opportunity a full year later to test one of the five subjects a second time This man, age 38 years, height 189 cm, and weight 51 kg, had kept himself constantly sugar free throughout the year and had lived on a daily intake of 940 calories His diabetes is of about eight years standing He, of course, did but little physical work, however, during the day, he is always dressed and about, employing half his time as a locksmith During the year he had gradually lost about 1 kg in weight but his fasting blood sugar was 0.10 per cent as compared with 0.23 per cent one year before Otherwise he appeared unchanged He spoke of feeling physical weakness, especially in the knees at stair climbing, and of being very sensitive to cold Comparing the measurements of December, 1920, with those made in January, 1922, we find that in only one test (station) did he do as well on the latter date In this there seemed to be almost no change In

four other tests, he showed some decrease in efficiency, ranging from 5 to 27 per cent, judged on the performance of his former record. The testing on the latter date was done very thoroughly and occupied two different mornings separated by two days so that we are quite confident that the later results do not misrepresent his condition. Hence, we must conclude that he now shows a loss of about 10 per cent in neuromuscular efficiency as compared with his condition a year ago.

DISCUSSION

We have found objective justification for the complaints of loss of memory and of ability to concentrate attention mentioned frequently by persons suffering from diabetes. The old and well established mental associations, such as are involved in doing simple addition of numbers seem but little influenced. But new tasks which demand immediate retention and recall, with little reference to past experience, are the ones which suffer and at which the patient finds himself below his former ability. There appears to be no marked increase in the errors which the diabetic makes in his work as compared with the normal person but rather a loss of speed, a decrease in the span, or amount that can be grasped at one time. That the change is chiefly in the nature of a retardation of the neuromuscular processes is indicated by those tests which more especially involved the muscles. In these we have found that the eye requires more time to turn and to react, that the fingers cannot make as many taps in a given interval, nor can the hand as accurately pursue a moving object. To what extent this retardation may be due to discouragement or mental depression on the one hand or specifically to the diabetes, as such, on the other, it is impossible to state. If we had available similar observations for groups of patients suffering with other diseases it would be possible to more satisfactorily make an appraisal of the influence of diabetes as compared with other conditions. There is clear evidence that with treatment, most of the individuals tested showed rapid improvement on the psychological side.

If we say that the diabetic is below normal in his neuromuscular efficiency, it may also be pointed out that few persons work to the limit of their powers, and that few situations in every day life demand or stimulate the laboratory grade of performance. While memory span and muscle movement speed are of fundamental importance for the activities of life, still there is a rather wide margin and undoubtedly very many diabetic individuals will be able to do as much light physical or mental work as is actually done by many normal men and women. In other words, while the diabetic is not at all fitted for racing in top-notch competition, still he is fairly well off for living comfortably and usefully.

It was found in the Nutrition Laboratory research on the effects of low diet that men living on one half to two thirds of their normal ration were able to do their college work and in some cases make even higher grades than before so it is quite possible that many diabetics will not experience from a reduced diet any marked change in their ability to perform their usual duties

SUMMARY

1 Diabetic patients frequently complain of poorer memory and power of attention, but objective proof of this has been lacking

2 By certain psychologic tests applied in such cases as well as to suitable controls it was found that diabetic patients with hyperglycemia and glycosuria at the beginning of treatment show a decrement of about 15 per cent or more in memory and attention tasks. The loss is in amount rather than in quality

3 With treatment the diabetic improves rapidly in his psychologic status, approaching but not quite reaching normal

4 In accuracy and quickness of movements five treated diabetics, each case of long duration, were 20 per cent below normal

EXPERIMENTAL OBSERVATIONS ON THE LOCALIZATION OF THE PAIN SENSE IN THE PARIETAL AND DIAPHRAGMATIC PERITONEUM

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CHICAGO

Pain is, perhaps, the most important evidence on which we base our interpretation and diagnosis of abdominal disease. So whatever contribution may be made to the better understanding of abdominal pain, its origin, nature, and localization, is of direct interest to the clinician.

Our present knowledge of sensation in the abdomen and its viscera is due largely to the careful and ingenious observations during laparotomies of Lennander¹ and Sir James Mackenzie². These observers are agreed that the hollow viscera and omentum give no sensation response to heat or cold, to cutting or clamping.

Lennander found that the parietal peritoneum was sensitive to irritation, especially when inflammation was present. This pain sense he explained by the rich supply of cerebrospinal nerves to the parietal peritoneum and its subserosa, in contrast to the sympathetic nerve supply of the insensitive viscera. From these premises he contended that all visceral pain was the result of inflammation and traction on the parietal peritoneum. Ross,³ however, has furnished convincing proof of a true visceral pain (splanchnic) induced by tension of the hollow organs, and in addition to this the somatic pain originating in a sensitization of the posterior spinal roots and a radiation of painful sensations along the course of the corresponding spinal nerves to the skin and deeper tissue layers.

The peritoneal membrane lining the abdominal wall has received less attention from experimenters than the viscera, while the peritoneum covering the under surface of the diaphragm, because of its inaccessibility has remained almost "terra incognita" to the surgical explorers who have been interested in charting areas of sensation by direct experimental methods. All animal experiments on pain are open to serious criticism of results obtained and, in any event, are far less trustworthy than experiments on human beings.

The parietal peritoneum in the immediate vicinity of laparotomy incisions made under cocaine anesthesia has been tested for pain with

1 Lennander, K. G. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **21** 125, 1910.

2 Mackenzie, J. *Symptoms and Their Interpretation*, London, 1909.

3 Ross, J. *Brain* **10** 350, 1888.

somewhat conflicting conclusions. For example, Lennander finds pain sense in the parietal peritoneum and the neighboring serosa. Mackenzie, working under similar conditions, believes that the parietal peritoneum is without sensation, but that the pain sense is acute in the subserosa lying just outside the peritoneum. This view is also supported by Hertzler⁴

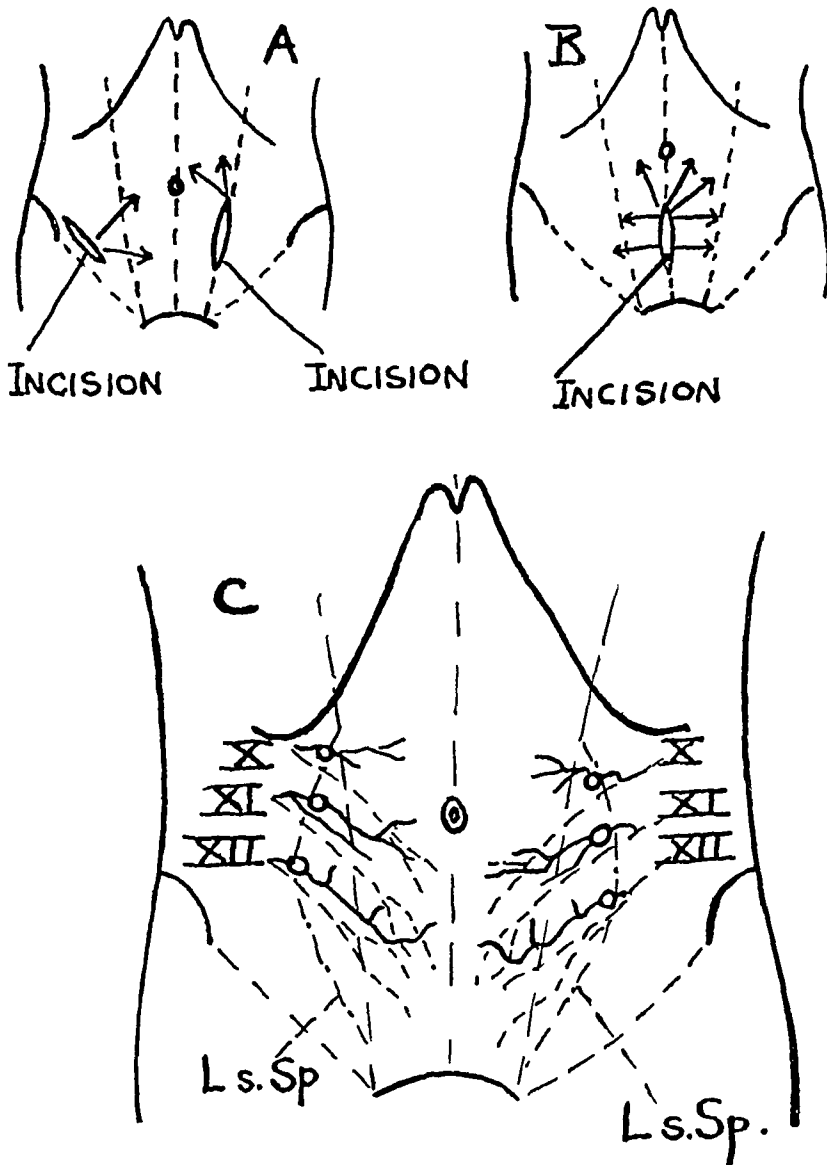


Fig 1—A and B, illustrating experimental method (Ramstrom), C, showing distribution of dorsal nerves to abdominal wall (broken line) and to peritoneum (solid line), (Ramstrom)

Subsequently, Ramstrom,⁵ the celebrated anatomist, carried out a series of experiments in this region in cooperation with Lennander. Ramstrom had already demonstrated the presence of the Vater-Pacini bodies in the anterior portion of the parietal peritoneum and proposed

⁴ Hertzler, A. E. *The Peritoneum* 1 24, 1919

⁵ Ramstrom. *Mitt a d Grenzgeb d Med u Chir* 13 314, 1908

to test this membrane for "pressure sense," which was supposed to be the specialized function of these nerve structures. The method of the procedure is illustrated in Figure 1. After the incision was made through the abdominal wall under cocaine, the neighboring peritoneal covering of the wall was tested for sensation by inserting a rubber glove covered finger and by a flat spatula, with varying degrees of pressure. He also used hot and cold instruments. He found that light pressure produced no sensation, strong pressure set up a cramp-like pain, cutting the parietal peritoneum caused a stitchlike pain. There was no response whatever to temperature changes. Ramstrom concludes that the parietal peritoneum has no pressure sense ("Drucksinn") and that the Vater-Pacini bodies, therefore, are not specialized structures for this sensation. Also, the sense of heat and cold is lacking. Finally, the parietal peritoneum is richly endowed with pain sense.

The chief purpose of our experiments was to determine the localization of pain from stimulation of the parietal and diaphragmatic peritoneum.

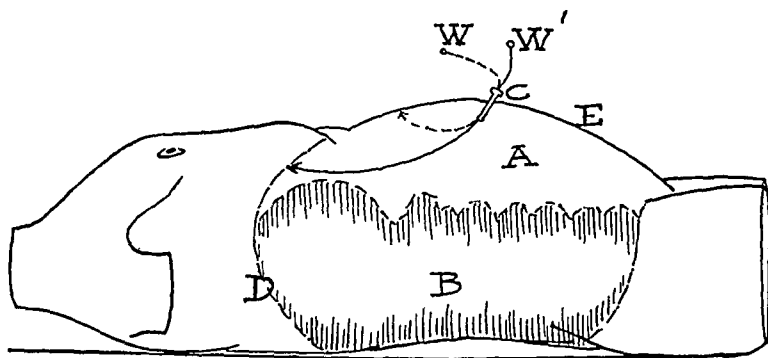


Fig 2—Schematic drawing to illustrate method of procedure. A Air in abdominal cavity. B Abdominal viscera depressed by the air. C Cannula or trocar through abdominal wall (E), into abdominal cavity. Trocar freely movable in all directions. D Diaphragm. W and W' Wires used in testing.

PERSONAL OBSERVATIONS

Our experiments were carried out by a method previously employed by one of us in the study of sensation in the pleural cavity. After partially anesthetizing the skin with ethyl chlorid, a trocar is inserted through the abdominal wall until the end moves about freely. The point is withdrawn and through the cannula is passed a long silver wire, one end beaded and smooth, the other end relatively sharp. Each end is slightly curved in order that it may more easily be brought in contact with the abdominal wall. In our earlier experiments patients with ascites were chosen because the fluid distended the wall and facilitated exploration. Recently, however, we have employed the method of injecting air, which has proven harmless in the hands of the roentgenologists. As will be seen in Figure 2 the air forces the hollow viscera to the bottom of the cavity, leaving a large domelike

area free for testing. The air also fills the subphrenic spaces and permits the passage of the wire to the under surface of the diaphragm, a region not accessible in ascites.

PROTOCOLS

EXPERIMENT 1 (Fig 3)—Observations were made during drainage of ascites in a case of cirrhosis of the liver. The wire end came in contact with the viscera without causing sensation. Several points on the parietal peritoneum were touched from 3 to 5 inches lateral and above the cannula with enough pressure to locate the tip by the observer's touch. The patient complained of "pain like a needle puncture" and with eyes closed localized the spot by touching the skin with the end of his finger. The patient's localization was usually a little below the actual point of irritation, but always within a radius of one-half inch. Pressure toward the flanks against the parietal wall caused a more diffuse pain.

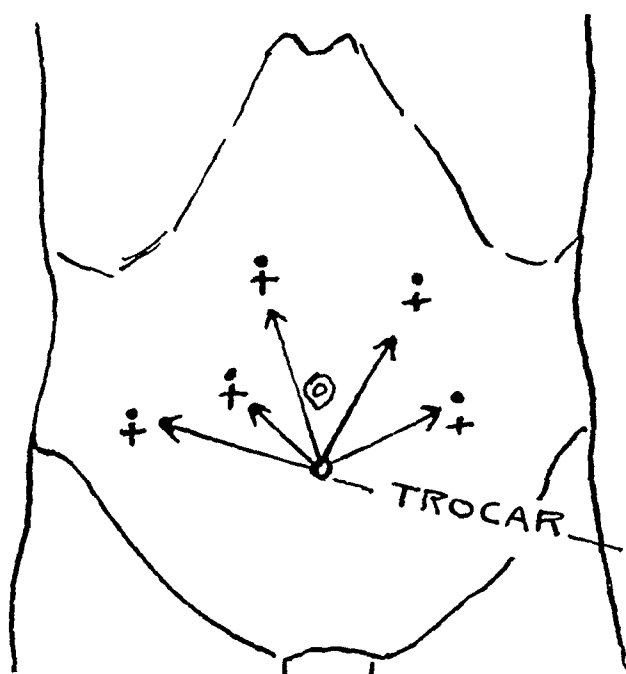


Fig 3—Experiment 1. Showing areas of parietal peritoneum stimulated by a wire passing through cannula. \odot = actual point stimulated, $+$ = localization of pain by patient, arrows show direction of wire.

EXPERIMENT 2 (Fig 4)—Patient with ascites. Wire passed along parietal wall in direction of arrows. Beaded wire end caused no feeling unless tip was pressed with considerable force. Rough end caused pain at points indicated of sharp character and localized by patient in close proximity to the point of contact.

EXPERIMENT 3 (Fig 5)—Case of ascites. Beaded end of wire entangled in viscera caused cramplike pain on movement, but none by superficial contact. Rough end of wire followed the parietal wall freely for some distance on both sides and above the navel. Contact with slight pressure or gentle movement over the parietal peritoneum produced sharp pain which the patient localized with remarkable precision close to the actual site of stimulation.

EXPERIMENT 4 (Fig 6)—Ascites from cirrhosis of liver. Conditions favorable to free exploration with wire. Localization by patient always within three-quarters inch of point stimulated.

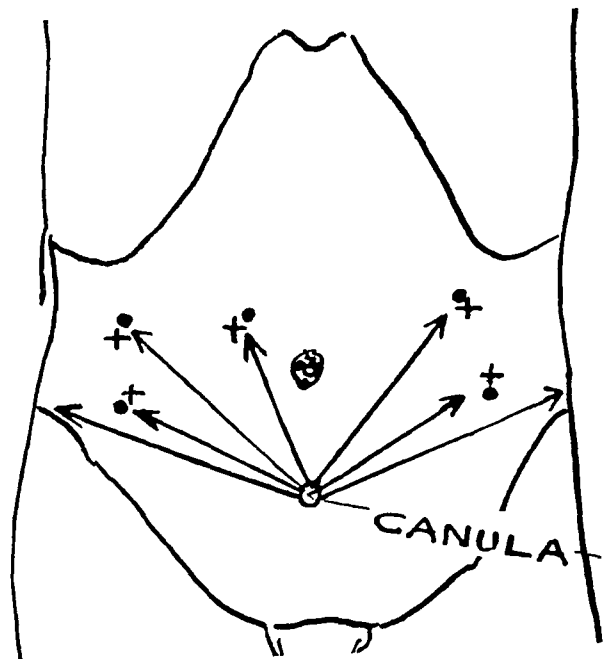


Fig 4—Experiment 2

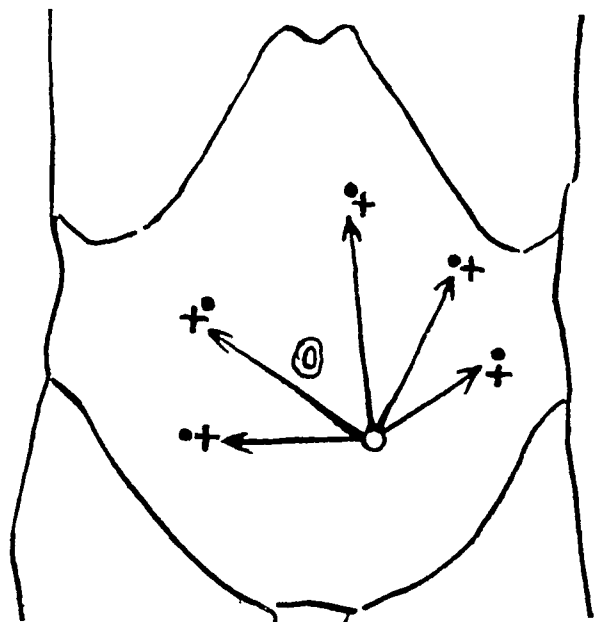


Fig 5—Experiment 3

EXPERIMENT 5 (Fig 7) —Patient had early tuberculous peritonitis No fluid obtained by puncture Filtered air slowly forced into the cavity until 3,000 c c had entered The abdominal wall was thin and tympanitic over all of the anterior aspect and well down in the flanks To prevent escape of the air, a strip of adhesive tape was stretched over the opening of the cannula and the wire passed through the tape into the cannula and abdominal cavity The silver wire was passed with ease along the inner abdominal wall in the direction of the arrows, the point being readily detected by the palpating finger and even with the eye Slight pressure with the beaded point produced no sensation Similar pressure with the rough point caused a sharp pain like a stitch Gentle lateral motion of the point produced a similar and more severe pain The localization of the pain by the patient was always within a radius of one-half inch from the point irritated

EXPERIMENT 6 (Fig 8) —Patient was a thin subject with no pathologic condition of the abdomen except a scar from a laparotomy performed two years ago for removal of pus tubes About 4,000 c c of air was introduced The results of irritating the parietal peritoneum with the wire were similar to

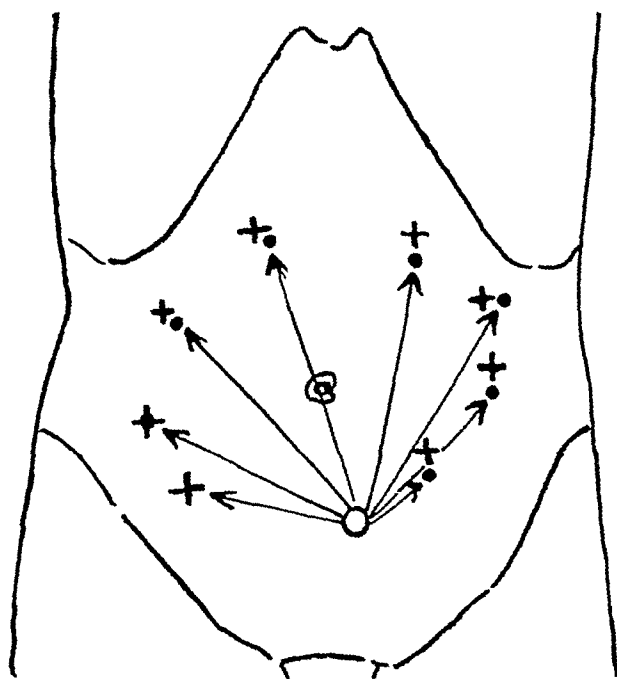


Fig 6—Experiment 4

those obtained in previous experiments When the wire came in contact with the adhesions beneath the scar and enough pressure exerted to produce displacement or stretching, the patient complained of a dragging painful sensation in the region of the scar tissue

EXPERIMENT 7 (Fig 9) —Patient had a very thin fat layer over the abdomen and no abdominal disease After puncture, more than 4,000 c c of air was introduced, with resulting tympany over the whole abdomen and even over the liver and spleen The wire tip could be followed readily by the eye as it passed along the inner wall The localization of pain was made with the same accuracy over the upper parietal peritoneum as in previous experiments The wire could be seen passing upward to the left costal border until it disappeared beneath the ribs About 2 or 3 inches above this point within the mammary line the beaded point came in contact with the diaphragm (central portion) Moderate pressure caused a sharply localized pain at a point situated over the middle third of the trapezius ridge When the rough tip of the wire was brought in contact with this region even slight pressure or a lateral motion set up pain of great intensity over the spot in the neck This spot

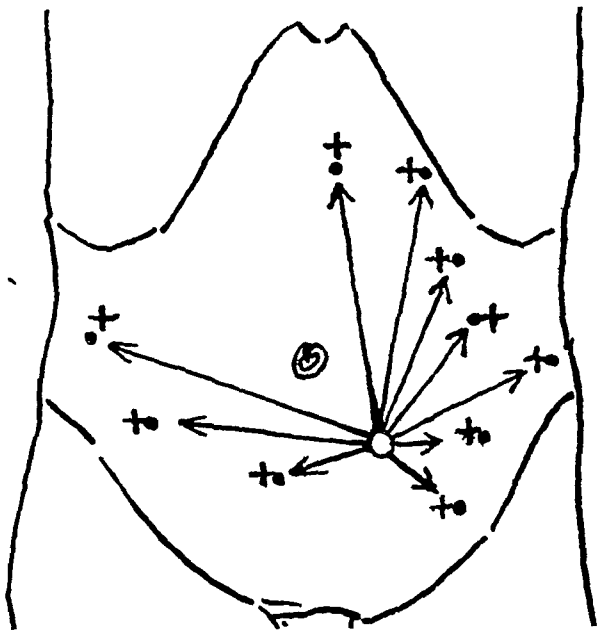


Fig 7—Experiment 5

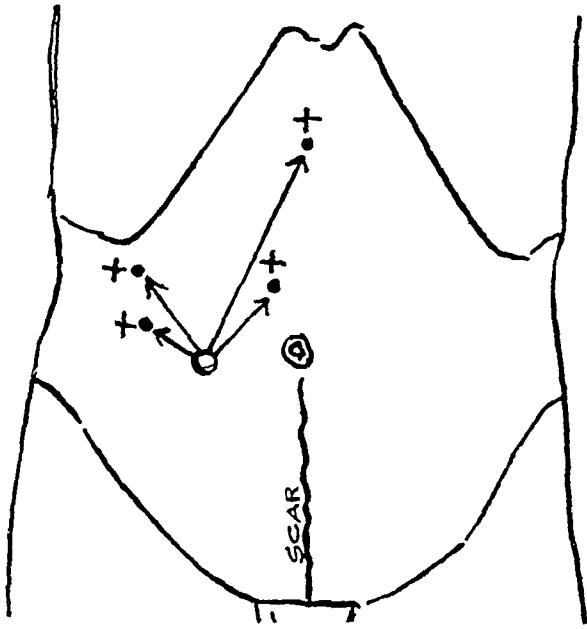


Fig 8—Experiment 6

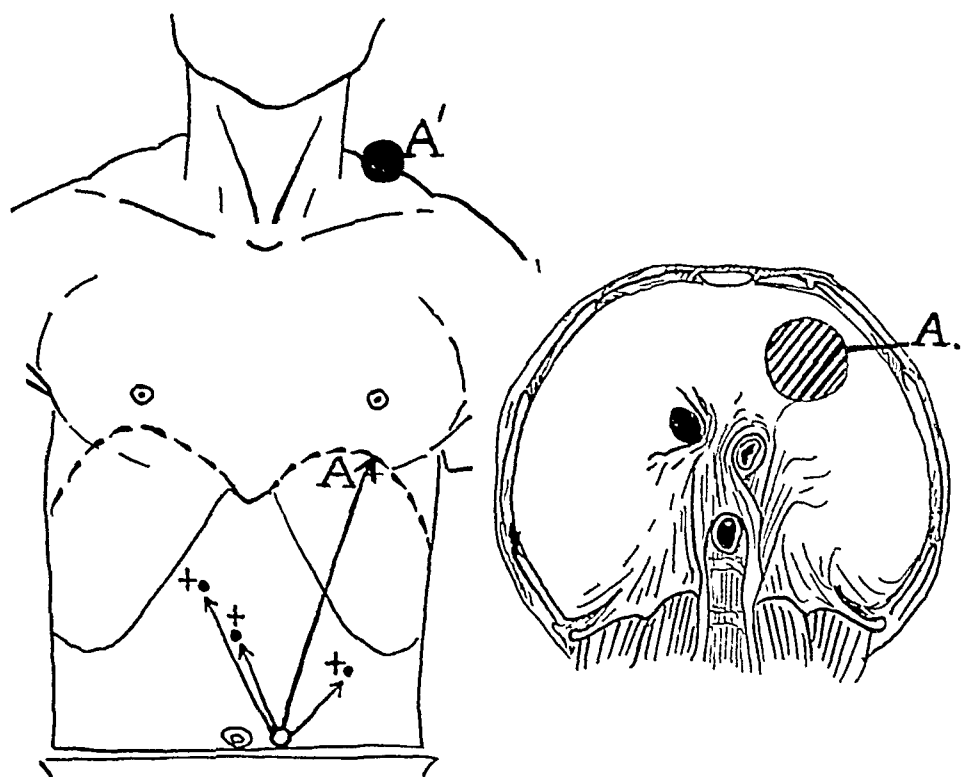


Fig 9—Experiment 7 Upper figure showing stimulation of parietal peritoneum and of the under surface of the diaphragm (A) with resulting referred pain in neck (A') Lower figure showing under surface of diaphragm, and region (A) stimulated

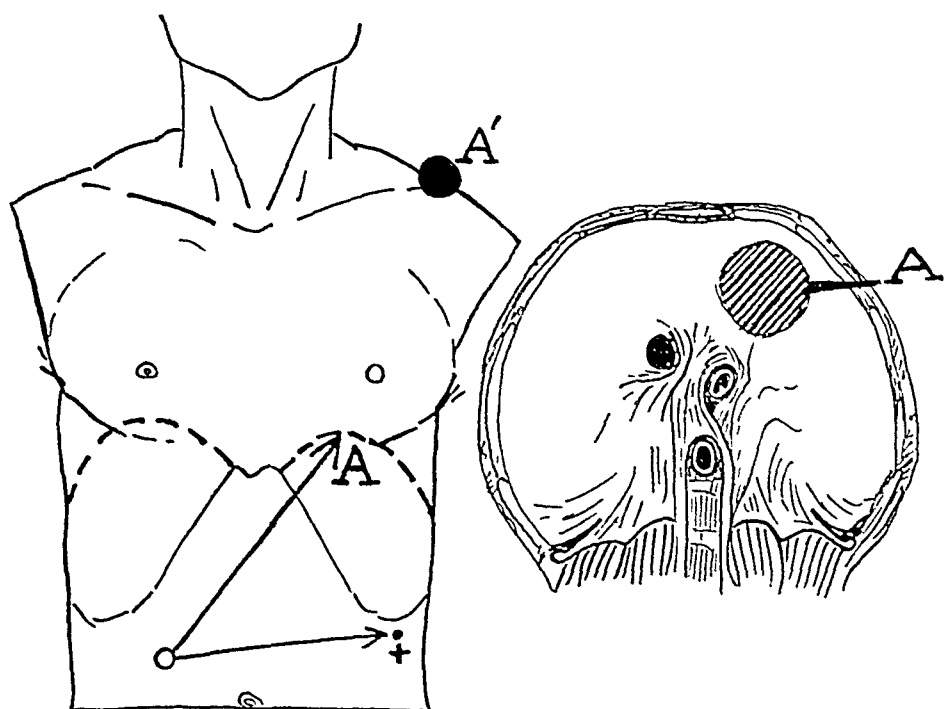


Fig 10 — Experiment 8 For explanation of symbols see caption under Figure 9

of referred pain did not change its location with shifting of the wire point over an area of the diaphragm 2 or 3 inches in diameter. As the wire was drawn down below the costal border on to the abdominal wall the pain in the neck ceased and the patient localized the pain over the portion of the abdomen corresponding to the point of wire.

EXPERIMENT 8 (Fig 10) —The patient was thin, with no abdominal symptoms. More than 5,000 cc of air was injected, creating tympany over anterior aspect of abdomen and high up under the thorax. The rough end of the wire was passed along the inner wall to the costal border, then upward 3 or 4 inches until it came in contact with the dome of the diaphragm. On the slightest pressure the patient complained of sharp pain definitely localized at the outer edge of the trapezius ridge. This point was tender to pressure over the skin. Withdrawal of the wire was followed by slow cessation of the pain, eight or ten seconds passing before its complete disappearance. Later contact of the wire with the parietal peritoneum an inch below the costal border produced pain close to the stimulated point.

EXPERIMENT 9 (Figs 11 and 12) —This patient entered the hospital with a marked pneumoperitoneum, probably due to perforation of a gastric ulcer. As shown in Figure 11 there was a large collection of gas separating the

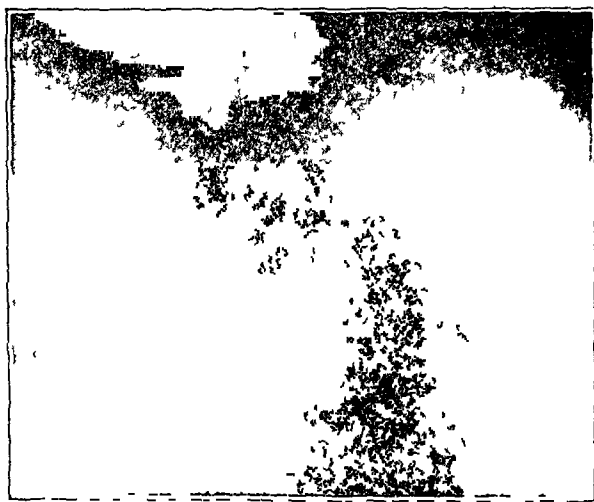


Figure 11

liver and spleen from the diaphragm. As the patient had no fever and was not very ill the following experiment was carried out in the erect position before the fluoroscopic screen. A trocar was inserted under the costal border upward into the air cavity over the liver. After the removal of the trocar the wire was run through the cannula and the escaping gas controlled by a rubber film. The beaded wire end could now be brought in contact at will with the greater part of the under surface of the diaphragm and be followed by the eye while the patient was asked to register sensation and its location. A light touch of the beaded end or gentle stroking motion produced no sensation anywhere. Firmer pressure produced pain (Fig 12). Over the peripheral margin, narrow anteriorly and broad posteriorly, the pain was diffuse and referred to the right costal border, the patient indicating the area with his hand placed transversely over the lower ribs and over the right hypochondrium. On removal of the wire this pain slowly disappeared. Over the central portion of the diaphragm firm pressure elicited a sharp pain over the outer third of the trapezius ridge. The patient indicated the spot with the tip of his finger and described the sensation as "the wire sticking into my neck." The patient complained if the observer pressed his finger on the skin at the spot

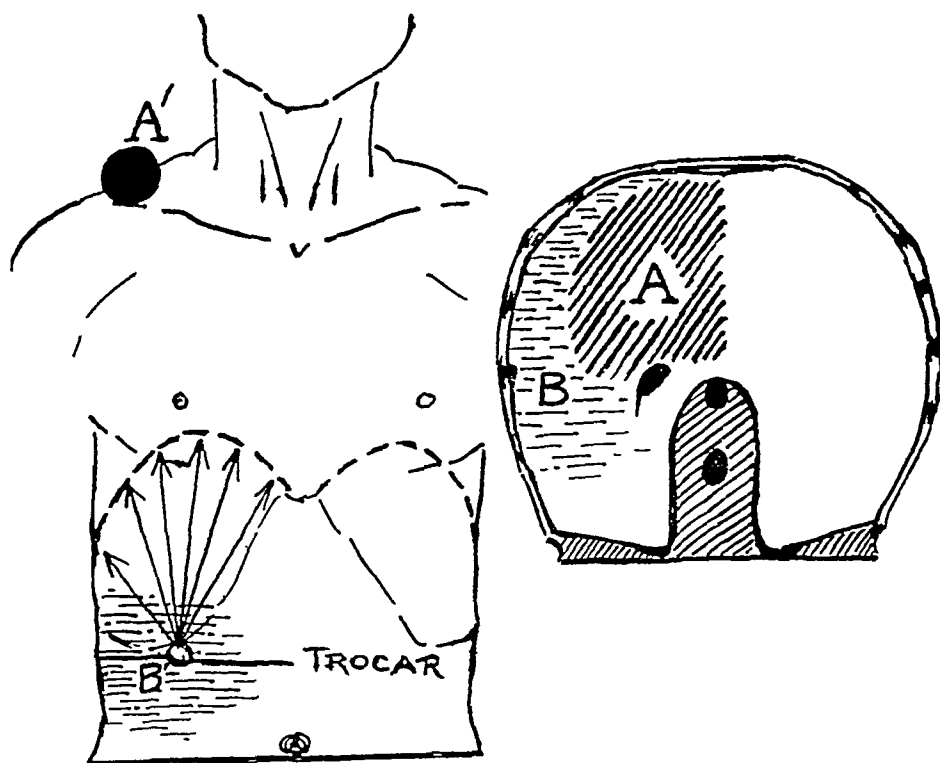


Fig 12—Experiment 9 Schematic drawing of Figure 11 Upper figure indicates points of stimulation of diaphragm with wire (patient standing before fluoroscopic screen) Lower figure (schematic representation of lower surface of diaphragm) showing approximate region (A), the stimulation of which caused localized pain at (A'), also approximate region (B), stimulation of which caused diffuse pain in region (B')

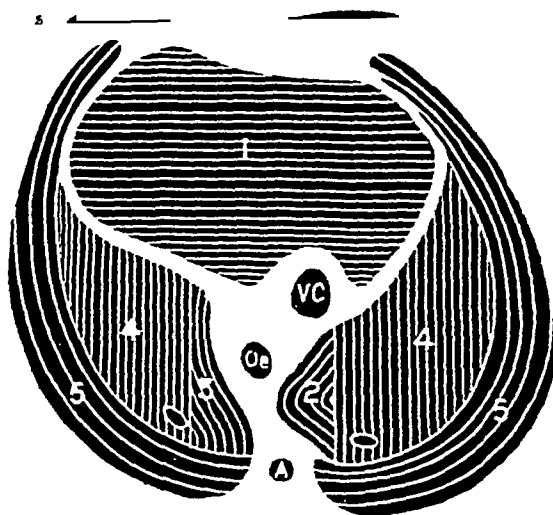


Fig 13—Diagram of the primitive diaphragm to show the several parts from which it is built up (After Broman) (Quain's Embryology, p 243, Fig 298) 1, pericardial part derived from septum transversum, 2 and 3, parts derived from the mesentery, 4, 4, parts derived from pleuro-peritoneal membranes between these dorsally and the mesenteric portions are the nearly closed pleuro-peritoneal openings, 5, 5, parts derived from the body-walls, 1, 2, 3, 4, 4, cover the cranial aspect (upper surface) of the liver

indicated. This pain also continued with decreasing intensity for several seconds after the pressure was removed. When the roughened wire point was used, the pain produced was much more severe, although the localization was the same as with the beaded point. After the above observations were completed the gas was allowed to escape and the patient went on to complete recovery.

The penetration of the phrenic nerve fibers into the peritoneal (as well as the pleural) covering of the diaphragm was demonstrated by Ramstrom, although their course could not be followed with accuracy.

The diagram of Quain⁶ (Fig. 13) shows that in the embryo a part of the diaphragm is a derivative of cervical myotomes which are displaced backwards as the diaphragm descends to its permanent level. These myotomes carry down in their descent portions of the third, fourth and fifth cervical nerves, fusing into the phrenic nerve and originally containing both motor and sensory fibers. We may reason that the motor fibers continue their function in activating the diaphragm muscle, while the sensory nerves through disuse cease to register localized sensations in the diaphragm. Under strong stimulation, however, these afferent fibers of the phrenic nerve retain their ability to carry impulses to the cervical cord and thereby give rise to referred pain in the neck.

The pain elicited from stimulation of the outer surfaces of the diaphragm is explained by the known distribution of the lower six intercostal nerves to the diaphragm. Afferent impulses through these nerves to the cord find expression in pain referred to the abdominal wall and lower thorax which receive their sensory supply from the corresponding cord levels.

The pain elicited in these experiments, in our judgment, arises from stimuli both in the peritoneum and the subserous tissues. The pain caused by pressure of the smooth point Mackenzie would attribute to stretching the nerves in the subserosa and the pain from the sharp point to tearing of the delicate peritoneal covering and penetration into the sensitive subserosa. It is easier, however, to assume that both structures are sensitive since both have the same supply of cerebro-spinal nerves. It is well to emphasize that the pain from the parietal peritoneum is always direct and not referred in contrast to that of the diaphragm.

SUMMARY

1 The parietal peritoneum, and its underlying serosa, so far as explored, namely, all the anterior median areas and the lateral areas as far as the anterior superior spines, are sensitive to pain from strong pressure of a smooth point or light pressure or lateral movement of a rough point of wire.

⁶ Quain. *Anatomy* 1 243, 1906

2 The pain elicited by stimulation of the parietal peritoneum is localized with considerable accuracy by the patient, the error being less than one inch

3 Our observations confirm the conclusions of Ramstrom and Lennander that the parietal peritoneum is devoid of pressure sense

4 The peritoneum covering the diaphragm is devoid of pressure sense as applied by light contact or stroking of a beaded wire point. But to strong pressure with a beaded point or light contact with a rough point it is acutely responsive to the sense of pain

5 The localization of pain from stimulation of the diaphragmatic peritoneum is never in the diaphragm itself. It is always referred to some distant part. Stimulation of the outer margin causes diffuse pain over the lower costal region and subcostal abdominal wall. Stimulation of the central portion produces pain over a sharply limited point somewhere along the trapezius ridge. These impulses are doubtless carried by afferent fibers of the phrenic nerve to the cervical cord and thence referred to the neck by the sensitized cutaneous nerves of the fourth cervical segment. This pain has not been observed along the course of the phrenic nerve itself

OSTEITIS DEFORMANS IN MONKEYS*

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Osteitis deformans, or Paget's disease, is a chronic constitutional process usually involving all the bones of the adult skeleton. It affects most severely the bones of the cranial vault and the long bones of the extremities. In contrast, the small bones of the face, hands, feet and joints are little, or not at all, involved. It is characterized by extensive absorption of compact bone and an excessive production of abnormal bone substance, fibro-osteoid tissue which, while soft and spongy, shows on roentgen-ray examination a definite calcification, and on chemical analysis a high calcium and inorganic content.

Paget¹ described this condition in 1876 in a paper that is still the most impressive on record. Following his communication many single and groups of cases were reported, until today approximately 350 cases are on record. As a fully developed entity it is still, however, classed among the rarer diseases of mankind. Jefferson Hospital had three cases in 30,000 admissions, Johns Hopkins, three in 38,000. When advanced, the picture is so striking and typical that it would be impossible to overlook it, but early cases or those with limited involvement cannot easily be and probably are not detected. It is very possible, therefore, that statistics do not represent the prevalence nor the wide distribution of the disease. It is for this reason that I wish to report these cases in monkeys.

Jonathan Hutchinson² found in an old Egyptian tomb a parietal bone which grossly and microscopically was osteitis deformans. This specimen, now in the College of Surgeons in London, is probably the earliest specimen on record. Waterhouse,³ Paget,⁴ Wilks,⁵ Goodhart⁶ and others collected authentic cases in collections of old bones in museums. Butlin⁷ included the Neanderthal man as an example, basing his diagnosis on the marked porosity of the bone, excessive development of the superciliary ridges, and the deep depressions for the Pacchionian bodies and the blood vessels.

* From the Laboratory of the Philadelphia Zoological Society.

1 Paget. On a Form of Chronic Inflammation of Bones, *Med Chir Tr* 60 37, 1877.

2 Hutchinson, J. *Illustr Med News* 2 177, 1889.

3 Waterhouse. *Lancet* 1 1215, 1907.

4 Paget. *Illustr Med News* 2 181, 1889.

5 Wilks. *Tr Path Soc Lond* 20 273, 1868.

6 Goodhart. Quoted by Wilks, *Tr Path Soc Lond* 20 273 1868.

7 Butlin. *Lancet* 1 519, 1885.

Stegmann's⁸ investigation of the bones of the American Indians is the only available study of the disease in savages or semisavage tribes. He found several excellent examples.

In lower animals the reports are very few and are not available in the original. The abstracts and references show considerable confusion. The names osteitis deformans, osteoporosis, osteofibrocystica, osteodystrophica deformans, osteosarcoma, leontiasis ossia, etc., are used almost interchangeably. In 1901 Barthelemy⁹ described a condition, "Maladie du Son," in horses in which there was a marked enlargement of the head and of the epiphyses of the long bones. His cases were more allied to osteitis fibrosa cystica. Paget's disease always attacks the diaphyses of the bones and not the epiphyses. Goldman¹⁰ described typical examples of this condition in fowls. Jost¹¹ in one communication described a case in a horse which he says was identical with that condition described by Paget as osteitis deformans and by Virchow as leontiasis ossia. He also refers to similar cases in goats and monkeys. Rossweg¹² found it in goats. In wild animals the only suggestive article found was by Jost¹³ but the description was probably of an osteoporosis and craniosclerosis which occurred in a young lion and a monkey. All these communications deal with either the domesticated animal or animals in captivity.

The etiology of this condition is as obscure today as it was at the time of Paget's first description. Prince¹⁴ thought it might be due to a defect in some peripheral nerve or nerve center, or to a tract degeneration. Cases have been reported in conjunction with a myelitis. There has been little, however, on which to base these suppositions. Heredity is supposed to be active in about 7 per cent of the cases. Paget felt that the process was at least on an inflammatory basis. He deduced this from the enlargement and the excessive production of an imperfectly developed structure with increased blood supply. Many felt that rickets, osteomalacia and osteitis deformans were all manifestations of the same disease. A bacterial cause was proposed by Arcangeli,¹⁵ who claimed the discovery of a diplococcus and improvement from a vaccine. Lancereaux and Richards¹⁶ felt that focal infection played a profound rôle in the etiology. However, all other observers fail to isolate an organism from the bones or to get improvement from removal of foci.

8 Stegmann. *Wien klin Wchnschr*, 1905

9 Barthelemy. *These de Lyon*, 1901

10 Goldman. *Verein Freiburger Aerzte*, May 30, 1902

11 Jost. *Arch f Wiss u prakt Tierh* **36** 652, 1910

12 Rossweg, F. *Vet Med Inaug Diss*, Giessen, 1913

13 Jost. *Arch f Wiss u prakt Tierh* **39** 164, 1913

14 Prince. *Tr Assn Am Phys* **17** 392, 1902

15 Arcangeli. *Rev ospedal*, Roma **5** 563, 1915

16 Lancereaux. *Traite d'Anat Part*, 1883

The more interesting theories go back to perversions of internal secretions, pituitary, parathyroid, etc. Higbee and Ellis¹⁷ say, in relation to the neurotrophic theory, that "if the neurotrophic mechanism governs metabolism and is influenced by the activity of the ductless glands, there is considerable likelihood that its disturbance may be found to be the cause."

Da Costa¹⁸ believes the disease to be a disorder of bone metabolism probably dependent on the absence or perversion of some internal secretion. There is much evidence on hand to prove that disorders of the ductless glands do influence bone metabolism, and changes in these glands have been reported in cases of Paget's disease, although the findings and lesions have been far from uniform or distinctive, and have not been confined to one gland. Eight cases were reported as possibly being hypothyroid conditions, pituitary changes were found in three, suprarenal changes in one, parathyroid reported missing in two, three had sclerotic thyroids. Many reports make no mention whatever of the glands of internal secretion.

Da Costa interprets the retention of calcium, phosphorus and magnesium, with the sulphur loss found in these cases, as indicating a stimulated osseous or osteoid formation, accompanying the resorption of a highly sulphurized organic matrix. In the course of this calcification procedure, he supposes that a certain quota of the sulphur of the matrix is replaced by other elements, a process which must entail retention of calcium, phosphorus and magnesium, and increased elimination of sulphur. He shows the close parallelism between the mineral metabolism of a growing boy, a case after parathyroidectomy, and a case of osteitis deformans, and suggests that this depends in some way, either on the absence or on the perversion of some internal secretion, possibly the parathyroids, which controls calcium exchange in the body. From some cause, substances arise which have the power to abstract calcium from the body tissues, the abstraction of these salts being the first step in the production of the disease. This theory of Da Costa's most satisfactorily describes the history of the monkeys which we wish to report.

REPORT OF CASES

In the Laboratory of the Philadelphia Zoological Society, among 6,570 consecutive postmortems, three cases of osteitis deformans have been found. (1) Red woolly monkey, (2) black spider monkey, (3) brown cebus monkey. This actually represents all cases giving even

¹⁷ Higbee and Ellis. *J. M. Research* 24 43, 1911.

¹⁸ Da Costa, Funk, Bergeim and Hawk. Publication from the Jefferson Medical College and Hospital 6 1, 1915.

a suggestion of this condition, because in the postmortem examinations in this laboratory, every skeleton receives really careful inspection

CASE 1—The first monkey received Nov 25, 1919, was a particularly active specimen and as far as we could determine, a perfectly healthy adult animal. He passed the tuberculin test and was placed on exhibition. In April, 1920, he was first reported as being crippled and in June, 1920, he was removed to the laboratory. At that time the long bones of the legs and arms were bowed anteriorly and laterally, the degree of the curvature making the hands and feet seem disconnected. The monkey could stand, but made no voluntary effort to do so. There was evidently some pain, although it could not have been at all severe. He resented handling, especially of his arms or legs. His head was rounded, resembling that of a baby. His eyes were protuberant, suggesting an exophthalmos. The maxillary bones were excessively thick so that his mouth could not close and the monkey drooled saliva. His blood on admission to the infirmary in May was hemoglobin, 89 per cent, erythrocytes, 4,370,000, leukocytes, 5,800. One week before death it was hemoglobin, 54 per cent, erythrocytes, 2,860,000, leukocytes, 6,000. The carbon dioxide combining power of the blood (Van Slyke method) was low, according to human standards approaching an acidosis, alkali reserve (Marriott method) also confirmed these findings; they were also noticeably low when compared with apparently normal monkeys. Routine urine examination showed a constant trace of albumin, hyaline and granular casts, and an excess of indican. There was at no time a Bence-Jones protein reaction. He had a constant slight diarrhea with some flatulence. The semifluid, constantly acid feces presents a preponderance of gram-positive organisms. His appetite was fair and he showed a marked craving for lime, eating plaster from the walls when he could get it. Because of this desire for lime, he was given a salt mixture to see if it would have any effect on the bone condition. The mixture was the following: sodium chlorid, 0.874 gm, potassium chlorid, 0.548 gm, calcium acid phosphate, 3.608 gm, calcium lactate, 0.386 gm, magnesium citrate, 0.848 gm, potassium citrate, 1.953 gm. This mixture the animal ate with avidity and seemed more comfortable while taking it; other than that no change was noted.

An inorganic metabolism was attempted in the ordinary diet, and in the diet plus the salt mixture. Under the conditions at our disposal this was not entirely accurate, but showed such marked variation from the normal osteomalacic animals reexamined, and such a marked correspondence on the four separate four day periods of each intake, that it seemed acceptable. The result of this investigation on the first series of four day periods was

Intake		Feces Urine Total			Retention
Calcium	0.0280	0.014	0.0022	0.0162	0.0118
Magnesium	0.0640	0.034	0.0123	0.0463	0.0177
Phosphorus	0.1540	0.027	0.0430	0.0700	0.0840
Sulphur	0.1440	0.002	0.1680	0.1700	0.0260 (loss)

The result on the higher salt content was practically the same, the retention proportionately to the intake, was slightly less.

The diet for these small monkeys is two apples, two bananas, six small sweet potatoes with a lump of boiled rice about the size of an egg. The content of this diet has been found to be very low in calcium, sodium, chlorine and iron, while the potassium, magnesium and sulphur are high. To this diet lime water was added to increase its inorganic content.

The red woolly monkey died Aug 20, 1920, and was immediately posted. There was marked thickening of the frontal, occipital, and parietal bones, and of the upper and lower jaws. The increase in the size of the alveolar margins prevented the closing of the mouth, only the last four teeth could be brought into apposition. The enlargement of the mandibles encroached on the capacity of the mouth cavity. The skull, while decidedly thickened, did not enlarge at

the expense of the cranial cavity. There was a cervical and dorsal kyphosis. The chest was increased anteroposteriorly and contracted laterally. The bones were thick, bulky, and deformed.

CASE 2—The black spider monkey showed a general hyperplasia of the whole shaft of the long bones. She was much deformed by curvatures and swellings of the skeleton. Head enlarged, face deformed by swelling of the upper and lower alveolar process, jaws did not close, and the palatal bones were flattened, skull irregularly thickened, elastic but not soft, slight subperiosteal growth, and a section of the ulna showed a subperiosteal osseoid layer surrounding the old shaft. This tissue seemed to be very poor in lime salts, cutting without any grit. Marrow cavity was filled with a fairly firm, deep red marrow which did not bleed on section.

CASE 3—The third monkey, the brown cebus, showed exactly the same general picture but was less severely affected than the other two.

PATHOLOGY IN BONES

The more minute study of the bones of these monkeys shows a variety of pictures while preserving one general form. The skull is smooth, mottled by irregularly placed areas of congestion, it is asymmetrically thickened, differentiation between cortex and diploe, and between internal and external tables is lost, calcareous matter is absorbed and the resultant bone is soft, elastic, and porous, lacunae enlarged and lined with bone corpuscles and giant cells. Other areas show more dense bone, the reparative processes being more active in that the lamellae are wide, and the vascular spaces narrow. As a rule the compact bone is absorbed, the Haversian canals are more or less confluent and there is generally a marked increase of newly formed osteoid tissue. The ossifying periostitis obliterates the depressions for the cranial arteries and sutures. The skull cap becomes finely porous, cancellous and even cavernous. The spaces are filled with a soft red marrow-like material. The bones at the base of the skull are much less involved, the pericranium, dura, and brain are normal.

The long bones show interlacing narrow strands which are in some regions wide, in others narrow, or thin as in spongy bone. Large irregular cavities are present, and there is a disappearance of the compact bone and an encroachment on the medullary canal of a relatively dense new bone, with small irregular trabeculae surrounded by osteoblasts and a fibrous connective tissue which fills the outer trabecular spaces. The new bone is often both subperiosteal and myelogenous, the latter frequently gaining on the former. It is always soft and irregularly calcified. The general arrangement of the strands in the deep layers is longitudinal, but in the subperiosteal bone they are very irregular and almost at right angles with the central strands. In this new osseoid tissue cysts are frequent, varying in size from very small to rather large cavities filled with a cloudy gelatinous material. The picture here is very like osteitis fibrosa cystica. Endosteal cells proliferate and may fill up the narrow spaces so that solid masses of fibrous tissue result. Frequently the osteoid material shows fibrillae. The compact bone may be regular with well marked Haversian systems, toward the periosteum the cells may become scanty, the bone dense in structure, while toward the interior the cells are more numerous, and in the more cancellous portions the trabeculae become slender and far apart, here they may be covered by a single row of osteoblastic cells. The intertrabecular spaces are large, irregular and filled with a delicate alveolar tissue containing only a minimal amount of normal bone marrow cells, large capillaries, and no giant cells. There is no evidence of bone destruction or unusual osteoblastic activity. Periosteum may be of usual thickness while the bone immediately beneath is spongy. The sclerosis of the bone in its densest areas is entirely due to the ossification of spindle cells which have remained in the place of the original marrow of the bone. As a whole the bone is nowhere normal in amount or proportion but the small Haversian systems are properly made, the abnormality being chiefly due to cellular and

fibrous growth around the large lamellae which at times is normal in amount but usually much in excess. In places this consists wholly of fibroblasts, at others of giant and round cells, very suggestive of sarcoma.

All histologists apparently agree that Paget's disease starts as a resorption of already calcified bone. Von Recklinghausen believed osteitis deformans started as an osteomalacia resulting first in a marked reduction of cortex and followed by an inflammatory process in the osteomalacic areas, characterized by the formation of fibrous tissue. The changes in Von Recklinghausen's disease are mostly regressive in the fibrous marrow with the formation of gelatinous cysts and also progressive changes leading to the formation in the large bones of small red brown tumors of the nature of sarcomas, an exaggeration of the process found in Paget's disease. The main difference between Von Recklinghausen's and Paget's disease lies in the changes in the bone marrow, which are much less severe in Paget's disease.

Many of the cases of Paget's disease first come under observation for fractures, accidents common in osteomalacia but very rare in developed cases of osteitis deformans. Early cases all presented diarrhea, which was present in all the early human cases seen, and in all the cases reported in monkeys. This symptom was mentioned in fourteen of the cases reported in literature. It was also a symptom in primate osteomalacia. The diet of these monkeys was exceedingly low in those substances essential to bone development. Sherman has shown that calcium balance is regulated to a certain extent by the calcium ingested, and that when the diet is poor in this element, the output materially exceeds the intake, a fact which is immediately changed when the animal is put on a diet high in calcium. As far as we could find, there are no studies on the mineral metabolism of beginning cases of Paget's disease. It seems possible from the osteomalacic animals previously studied, that the low mineral and otherwise faulty content of the diet and the symptoms they produced might so disturb the chemical equilibrium directly, or through the neurotrophic mechanism, or through the perversion of the ductless glands, that the mere addition of lime water might entirely change the pathological picture. This is in accord with the histology. The initial histologic picture is always resorption of bone, a general decalcification, which later presents an irregular proliferation. The disease then progresses along different lines ending as an osteitis fibrosa cystica, Paget's, von Recklinghausen's, or other disease, dependent on the strength and character of the reparative stimulus and the organism upon which it acts.

This is also in accord with the probable chemistry of calcification. In osteomalacic monkeys there is a change in fecal bacteria to a type producing much acid and causing a probable drain on body alkalis.

There is also a lowered alkaline reserve and a diminished carbon dioxide carrying power of the blood. According to Wells,¹⁹ calcium is carried in the blood in amounts not far from the saturation point, and is held in solution by colloids and carbon dioxide probably in the form of an unstable double salt of calcium bicarbonate and dicalcium phosphate. The reduction of carbon dioxide in any area, or some unknown agency causes the precipitation of the calcium salts. The lowered carbon dioxide carrying power of the blood was present in one monkey when the heavy calcium content of diet was started, and other conditions, as the acid diarrhea, were present which very probably constantly drained the fixed alkalis of the body.

These cases are of interest (1) because they are typical examples of Paget's disease as it has been described in man both clinically and pathologically, (2) because they show the same general type of inorganic metabolism that was exhibited in man, (3) because of the alkali hunger shown by one of the monkeys and by two human cases, a hunger which was severe and which preceded the deformity and disappeared after the deformity was established, (4) because the disease developed in animals fed on a diet insufficient in its inorganic and vitamin content, to which an excess of calcium was added.

From this study it seems possible that Paget's disease may be just one stage in a deficiency disease. It may be a reparative response (1) through a disordered neurotrophic mechanism, (2) through the perversion of the calcium governing glands which have been disordered by an improperly balanced diet, or (3) through the addition of an excess of calcium to the diet of an animal whose body fluids were unable, through previous faulty diet or other disorders, to hold it in solution.

19 Wells. *Chemical Pathology*, Philadelphia, W B Saunders Company, 1918

CHOLERA ACIDOSIS AND ITS THERAPY^{*}

M TSURUMI, M D, AND T TOYODA, M B

DAIREN, MANCHURIA

Acidosis is now generally known to be present in various diseases, such as diabetes, nephritis, uremia, and when violent diarrhea and vomiting occur clinically, there is also a rapid decrease in the body fluids. In most cases of cholera, the victim falls into a state of temporary inanition, and in consequence of the action of the toxin on the kidneys, so-called cholera nephritis very often develops. The decrease of blood alkali and the accumulation of acid in the body, make the existence of acidosis a certainty.

Sellards noted the remarkable tolerance of the urine to alkali, while Rogers observed a notable decrease of alkali in the blood.

During the cholera epidemic of last year, 529 cases were treated in the Dairen Isolation Hospital. Owing to a lack of apparatus Van Slyke's method for the determination of acidosis could not be employed. Traube's quinin method was resorted to instead, and the stalagmometer was employed. Placing the blood plasma to be tested in a solution of hydrochlorate of quinin liberates the quinin through the action of the alkali in the plasma, and the quinin so liberated will lower the surface tension of the solution so that it assumes a form somewhat resembling colloid and possesses a large molecular weight. Some of the mixture is allowed to drip by means of a stalagmometer, and the amount of alkali in the blood is determined by the number of drops. The greater the amount of alkali present, the lower is the surface tension of the mixture, and, also, the greater the number of drops. On the contrary, if the number of drops is small, it is assumed that the alkali in the blood is lessened, which state is termed acidosis.

The stalagmometer we used delivered 55.9 drops of distilled water at 20 C with the maximum range of about 0.1 drop. As a difference of 0.15 drop was found to correspond to a rise or fall of 1 C, the number of drops obtained from the experiment was calculated as for a temperature of 20 C.

DETERMINATION OF ACIDOSIS IN CHOLERA CASE

1 *Determination of Alkali in the Blood of a Person in Good Health*
—Five young men and five young women, all in good health, were tested for blood alkali between 3 and 4 p. m. An average of 68 drops (with 68.6 for the highest and 67.5 for the lowest) was obtained.

^{*} From the Dairen Isolation Hospital.

Although the number of instances is too few to be used as a control, the average obtained was thought to be near enough to the average of 69 drops obtained by Onodera in 200 cases

2 *Determination of Alkali in the Blood of Cholera Cases*—Forty-nine cases of cholera subjected to the alkali test (including two cases in which cholera vibrios were not found) were divided into three classes (1) mild, (2) medium and (3) severe—according to the conditions present at the time of withdrawing the blood, which was just after their admission to the hospital. All the patients, except two, were young adults. The exceptions were aged 12 and 16 years, respectively. (a) Nineteen mild cases (none resulting fatally) gave an average of 67.9 drops, showing little decrease from the average of 68 drops for normal persons. This indicates that, as far as the alkali in the blood is concerned, there is but little difference between mild cases of cholera and normals. (b) Eleven medium cases (including one fatal case) gave the average of 67.7 drops, being less by 0.3 drop than for normals. However, it can hardly be said that any considerable decrease in alkali in the blood was observed in these cases. (c) Among nineteen severe cases (including thirteen fatal cases) with an average of 67 drops, seventeen showed a remarkable decrease, the average being 66.6 drops, being 1.4 drops less than for the average for normals. It may be added that most cases below 66 drops ended fatally. In other words, the decrease in the number of drops appeared to have some definite relationship to the prognosis.

3 *Alkali Injection and Number of Drops*—The alkali used was sodium bicarbonate. It was dissolved in saline solution up to from 25 to 30 per cent, sterilized, and from 500 to 1,000 c.c. of this solution was injected intravenously. This injection was performed, when possible, immediately after or within a few hours after the patient's admission to the hospital. After the blood alkali has been determined, the operation was repeated, if necessary. These determinations of the alkali were made at intervals of one hour, one day, or several days. Of the twenty-seven cases, the number of drops or the alkali in the blood were increased in fifteen, the alkali was decreased in eight, and no change was noted in three.

When more injections were given, the increase in alkali was greater. Therefore, in many cases, the injection of the sodium bicarbonate solution caused a temporary or a permanent increase of alkali in the blood, and an improvement in the patient's condition.

Why did the number of drops decrease after the injection in certain cases? Probably because the acid generated in the body was present in such large quantity that even the injection of alkali did not cause a notable increase in the blood alkali.

TREATMENT OF CHOLERA

1 *Injection of Sodium Bicarbonate Saline*—There is no disputing the efficacy, to a certain degree, of the injection of immune serum and saline, but it is far from satisfactory. As stated, in cases of cholera, especially severe ones, the blood alkali decreases remarkably, causing the appearance of acidosis. Therefore, the injection of alkali, for instance, sodium bicarbonate saline, is rational therapy. The amount of alkali in the blood and the clinical symptoms may be considered to parallel each other, as a rule. In other words, the more the alkali increases, the greater improvement in the patient's condition. In cases which ended fatally, even the use of alkali in large quantities could not prevent the blood alkali from decreasing sharply, the urine being strongly acid, showing an increase of tolerance for alkali.

The mortality among those patients who received the sodium bicarbonate and among others who did not was as follows. Cases treated with sodium bicarbonate saline, forty-nine, fourteen deaths, or 28.4 per cent mortality. Cases treated with saline or serum-therapy or both, 480, 205 deaths, or 42.7 per cent mortality.

Making due allowance for the great difference in the number of cases of the two groups, the death rate in the first group was 14.3 per cent lower than the death rate in the second group. There is reason to believe that this lowering of the mortality rate can be carried still further. It is specially noteworthy that none of the patients subjected to the alkaline therapy died of the choleraic stupor or of uremia.

2 *Lack of Chlorids in the Body*—Quantitative tests for chlorids in the urine, were made by Moore's method in ten cases and showed that the quantity of chlorid decreased markedly as the patient's condition reached a very serious stage, and increased as he improved, gradually reaching the physiologic state. The quantity of chlorid contained in the urine of a healthy person is about 1 gm. In our patients, the average was only 0.2 gm. on the second day of the disease, 0.4 gm. on the fifth day, and 0.5 gm. on the ninth day.

It may be assumed that when the blood chlorid is not measured, its accumulation in the body must be reckoned with. However, when it is remembered that, according to Rogers, the blood chlorid of cholera patients is below the average normal, the injection of saline as a cure is based on rational grounds. Nevertheless, to prevent the removal of the saline injected it seems rational to use hypertonic saline, from 1 to 1.2 per cent above the physiologic percentage.

SUMMARY

1 The alkali content of the blood in mild cases of cholera is practically the same as in health. But in the severer, and especially in the very serious cases, a marked decrease of alkali is observed, leading to acidosis.

2 By the injection of alkali, the blood alkali in cholera cases is generally increased temporarily or permanently, that is to say, the number of drops by the stalagmometer (according to Traube's method) increases. The occasional decrease of the number of drops is believed to be due to the increased acid produced in the body and to the great increase of tolerance to alkali in consequence of acidosis in an acute form.

3 The mortality after the injection of sodium bicarbonate-saline in forty-nine cases was 28.4 per cent, while the mortality in 480 cases in which no alkali was given, but instead saline, or serum, or both, was 42.7 per cent, a difference in favor of alkaline therapy of 14.3 per cent.

OBSERVATIONS ON VITALLY STAINABLE RETICULATION AND CHROMATIC GRANULES IN ERYTHROCYTES PRESERVED IN VITRO*

O H PERRY PEPPER, M D

PHILADELPHIA

These observations were made with the object of determining whether the vitally staining reticulation of young erythrocytes persists or is lost in blood preserved in vitro. In this manner it was hoped to gain some further information concerning the effect of such preservation on the erythrocyte from the point of view of the value of such cells for transfusion purposes. If it could be shown that preservation of erythrocytes in vitro for several weeks or a month did not reduce the percentage of cells in which the reticulation could be demonstrated by vital staining it might, perhaps, be assumed that the preserved erythrocytes had not aged during the period of preservation and were from this point of view as suitable for transfusion as freshly drawn cells.

Rous and Turner¹ obtained the best preservation of human erythrocytes with three parts of blood in two parts of isotonic (3.8 per cent) sodium citrate in water, and five parts of isotonic (5.4 per cent) dextrose in water, and these observers² found that erythrocytes thus preserved in the cold for fourteen days can be used for transfusion and will apparently remain in the circulation and function satisfactorily. Kambe and Komiya³ came to the same conclusion after studying the effect of transfusion of erythrocytes preserved in vitro up to twenty days on the appearance of polychromatophilia in the circulating blood following hemorrhage. Polychromatophilia is a regeneration phenomenon and is seen in young cells only. As a rule, it appears in twelve to twenty-four hours after hemorrhage, reaches its highest point in three or four days and disappears in a week. It was found that transfusion of preserved cells prevented the appearance of this polychromatophilia just as effectively as did transfusion of fresh cells, thus proving the vitality of the preserved cells. This did not, however, give any evidence as to the durability of the preserved cells.

* From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.

1 Rous, P., and Turner, J. R. The Preservation of Living Red Blood Cells in Vitro, *J. Exper. M.* **23** 219, 1916.

2 Rous, P., and Turner, J. R. The Preservation of Living Red Blood Cells in Vitro, *J. Exper. M.* **23** 239, 1916.

3 Kambe, H. and Komiya, E. Transfusion Experiment with Red Blood Corpuscles *Am. J. Physiol.* **53** 1 (Aug.) 1920.

There is little known about the persistence of the reticulation in erythrocytes after removal from the body Key⁴ states that the reticular substance can be demonstrated in oxytated or defibrinated blood which has been shed for periods up to sixteen days if it be kept on ice No other statements on this subject have been found in the literature

In the present study rabbit and human bloods were employed The rabbits were rendered anemic by bleeding or by injections of sodium oleate in order to increase the number of reticulated cells Severe anemia was avoided for fear of altering the resistance or other characters of the erythrocytes, this point has not been sufficiently considered in experimental work The blood was obtained under sterile precautions and either defibrinated or added to the sterile dextrose citrate solution of Rous and Turner Samples were then placed in the ice box at 8 C and observed at intervals Other samples were incubated at body temperature The count of reticulated erythrocytes was made at the time of obtaining the blood All preparations were vitally stained with brilliant cresyl blue For other studies of the blood Wright's stain was used

Results—Defibrinated rabbits' blood kept in the icebox continued to have demonstrable reticulated cells for as long as one month After three weeks the number of reticulated cells decreased, and in some of the reticulated erythrocytes there appeared one or two small discreet granules staining blue with the cresyl blue, suggesting that the reticulation was disintegrating

Blood taken into 3.8 per cent sodium citrate solution almost always promptly showed a reduced number of reticulated forms as compared with the undiluted blood, but this varied considerably in various experiments Occasionally, with human blood in citrate solution no reticulated forms could be found while with rabbit blood the reticulated erythrocytes were not lost In one observation with rabbits' blood taken into 3.8 per cent citrate in the proportion of three parts of blood to two parts of citrate solution and kept in the icebox reticulated erythrocytes persisted in undiminished number for a week but had disappeared three days later Human blood usually continued to show a few reticulated forms and on one occasion these forms persisted for a month in blood which had been preserved by the Rous-Turner method Unger⁵ has shown that sodium citrate even in the low percentages employed in transfusion renders the erythrocytes more fragile, but there is no evidence that this increased fragility is in any way related

4 Key, J. A. Studies on Erythrocytes, with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch Int Med 28 511 (Nov.) 1921

5 Unger, L. J. Deleterious Effect of Sodium Citrate Employed in Blood Transfusion, J. A. M. A. 77 2107 (Dec. 31) 1921

to the disappearance of the reticular substance. Some years ago Pepper and Peet⁶ were unable to demonstrate any constant difference between the reticulated and the nonreticulated forms in their resistance to hemolytic agents but no observations were made with citrate.

Incubation at body temperature of blood in citrate solution resulted in such rapid hemolysis as to make examination unprofitable after twenty-four or forty-eight hours. Defibrinated blood, however, could be studied for a number of days during incubation at body temperature. The reticulated forms rapidly disappear under these conditions, for example, in one experiment the following figures were obtained for reticulated cells. At time of bleeding, from 6 to 7 per cent, seventeen hours after bleeding, 6 per cent, twenty-four hours after bleeding, 4 per cent, forty-eight hours after bleeding, 2 per cent, seventy-two hours after bleeding, none seen.

In this same blood preserved in this icebox the percentage of reticulated forms was undiminished at the end of three weeks. In no specimen of blood left in the incubator were fully formed reticulations found after forty-eight hours but in one instance a few remnants of the reticular substance were found after sixty-six hours incubation. One would hardly be justified in drawing any conclusion from this observation as to the probable period for which reticulation persists in young erythrocytes after they enter the circulation. It is probable, however, that the period is a short one.

In rabbits' blood preserved either in the icebox or at body temperature there appear within twenty-four or forty-eight hours in many of the cells shown to contain reticulation by vital staining with brilliant cresyl blue, one or more bright crimson spots. These number from one to, perhaps, six or eight, and vary in size from minute points up to perhaps a sixth of the diameter of the erythrocyte. In shape they are round or oval. Only when the blood has been stained with brilliant cresyl blue do they appear crimson, in the unstained wet blood they can be recognized as pale pinkish slightly refractile areas which disappear with the drying of the blood spread. With Wright's stain the spots do not take the stain but in the polychromatophilic erythrocytes there occur refractile irregular spaces which are apparently due to the same structures. In a dry preparation in which the reticular substance has been previously stained with brilliant cresyl blue these areas are seen as clear spaces often with the reticulation clumped around. With longer preservation the number of reticulated erythrocytes containing these crimson bodies increases and finally with the disappearance of the reticulated erythrocytes the crimson granules cease to be found.

⁶ Pepper, O. H. Perry, and Peet, Max M. The Resistance of Reticulated Erythrocytes, *Arch. Int. Med.* **12**: 81 (July) 1913.

These granules are in all probability the "substantia metachromatica" described by Cesaris-Demel⁷ in 1907 and much discussed sometimes under the term "chromatic granules of the reticular substance" in the German hematological literature since that date, especially by Schilling-Torgau⁸ and Pappenheim⁹. Key refers to them and states that they had not been previously mentioned in American literature. He and others have observed them in freshly drawn, vitally stained preparations especially of anemic blood. He suggests that they may be lipoidal in nature, a view first advanced by Pappenheim but Key argues that if so the granules should be visible as refractile bodies in the unstained cell. Key did not observe such refractile bodies in the unstained cells, but in the course of the present observation this was repeatedly done. They are undoubtedly not mitochondria nor do they resemble the vacuoles which frequently occur both in reticulated and nonreticulated cells. It would seem that their increasing frequency during the preservation of erythrocytes *in vitro* would make it probable that they are a degenerative phenomenon of young cells. This is the view originally advanced by Cesaris-Demel. Why they should occur chiefly, if not solely, in reticulated cells has not been explained.

DISCUSSION

These results do not allow many conclusions to be drawn. There is apparently no question that sodium citrate as employed in the Rous-Turner method interferes to a varying degree with the demonstration by vital staining of the reticulation of young erythrocytes. But this does not prove that the erythrocyte has been injured in any manner nor that its usefulness has been impaired. Some of the cells continue to show reticulation, and these may persist for as long as a month, which is as long as the blood is considered suitable for transfusion. Defibrinated blood kept at 8 C continues to show reticulated forms in undiminished numbers for about three weeks and this apparently argues against any aging of the corpuscles. On the other hand, the increase in the chromatic granules might be interpreted as a degenerative phenomenon and this supports the view originally advanced by Cesaris-Demel.

7 Cesaris-Demel, A. Studien über die roten Blutkörperchen mit den Methoden der Färbung in frischem Zustande, *Folia haematol* 4 (Suppl.) 1 (Oct.) 1907.

8 Schilling-Torgau, V. Ueber die Polychromophilie und verwandte Zustände, *Folia haematol* 11 327, 1911. Arbeiten über die Erythrozyten, *Folia haematol* 14 (Arch) 95 1912.

9 Pappenheim, A. Ueber Polychromophilie, *Folia haematol* 9 (Zentral Organ) 311 (June) 1910.

It would seem that the evidence on the whole was rather in favor of the view that preservation of the blood in vitro in the cold does not of itself age the erythrocytes and so perhaps does not make them any less useful for transfusion. This would agree with the findings of others. A suspicion is raised, however, that citrate may be injurious to the erythrocytes and this effect may be the same whether it is added to prevent clotting at the moment or for the purpose of permitting preservation in vitro. This also agrees with the other evidence concerning the use of citrated blood for transfusion as presented for example by Drinker and Brittingham¹⁰

¹⁰ Drinker, C. K., and Brittingham, H. H. The Cause of the Reactions Following Transfusion of Citrated Blood, *Arch Int Med* **23** 133 (Feb) 1919

THE EFFECT OF ATROPIN ON GASTRIC FUNCTION, AS MEASURED BY FRACTIONAL ANALYSIS

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AND
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DETROIT

A study of the literature is not at all convincing as to the effect of atropin on the stomach, especially its clinical effect on the human stomach. While on laboratory animals its effects seem to be quite definite, the reverse is true, according to the literature, when the drug is used in clinical medicine for the purpose of lessening spasm or reducing secretion.

Auer and Meltzer¹ assert that atropin causes paralysis of the vagus endings connected with the ganglia of Auerbach's plexus and that the action is on the myoneural junction. Cushny² states that the secretion of gastric juice has been shown to be diminished or entirely arrested by atropin, which paralyzes the termination of the secretory fibers of the vagus, and that the hydrochloric acid is more reduced than the pepsin or total fluid.

Zunz and Tysebaert³ found that in dogs, after a hypodermic of from 0.005 to 0.01 gm atropin per kilo of body weight, the stomach contractions were weak and diminished, the effect beginning in one half hour and lasting 5 or 6 hours. After smaller doses the movements were normal but the tone was less. Ginsburg and Tumpowsky⁴ gave from 1/80 to 1/40 grain atropin intravenously to dogs and found that it invariably inhibited contractions and counteracted the effect of pilocarpin and eserine, the action started in from 5 to 10 minutes and lasted for hours.

Smith,⁵ working with strips cut from different parts of the stomach of rabbits, cats and dogs, found that solutions of atropin sulphate, 1:1,000,000 and 1:100,000, invariably produced relaxation of longi-

*From the Medical Clinic of the Detroit Receiving Hospital

1 Auer, J, and Meltzer, S J. *Am J Physiol* **17** 17, 1906

2 Cushny, A R. *Pharmacology*, Philadelphia, Lea and Febiger, 1915, p 323

3 Zunz, E, and Tysebaert, J. *Action of Atropin Sulphate on Isolated Stomach and Intestine*, *J Pharmacol & Exper Therap* **8** 325 (June) 1916

4 Ginsburg, H, and Tumpowsky, J. *Control of Hunger by Drugs*, *Arch Int Med* **22** 553 (Nov) 1918

5 Smith, M J. *Action of Autonomic Drugs on Surviving Stomach*, *Am J Physiol* **46** 232 (June) 1918

tudinal, circular and oblique muscle fibers from all parts of the stomach Hecht,⁶ in work done on the surviving stomachs of rats, found a variability in the action of atropin due to the presence or lack of peristalsis inducing substances and of cholin in particular

Keeton, Luckhardt and Koch⁷ worked on dogs with a Pawlow stomach and found that 1 mg (0.12 mgm per kilo of body weight) inhibits secretion over a period of five hours and shows no toxic effects They found that from 50 to 80 per cent of the total secretion was arrested before the hydrochloric acid dropped The pepsin was also diminished

The laboratory work on animals would lead one to believe that atropin might have like results on man and would be a very valuable drug in clinical medicine However, the literature, while very scanty, is divided in opinion as to its value

Riegel in 1899 reported that atropin caused a decrease of hydrochloric acid and total juice after a test meal of one liter of milk Barclay⁸ states that belladonna often, but not always, relieves spasmodic contractions of the stomach by paralyzing the vagus and allowing unopposed action of the splanchnics

Rehfuss⁹ showed that large doses of atropin hypodermically causes a diminution of the psychic secretion and acidity, but never causes complete disappearance of the secretion Crohn¹⁰ measured the effect of the drug on the secretion and emptying time of the stomach by fractional analysis He found that 1/65 grain hypodermically one half hour after eating did not affect the motility but raised the average acidity from 32 to 76 degrees This, he states, was repeated on another patient with the same results In two cases, which had shown continuous interdigestive secretion, 1/65 grain hypodermically stopped the secretion, this secretion also ceased when the patient was fully atropinized by mouth, by giving 1 c c tincture of belladonna four times daily for three days, however, this procedure increased the digestive acidity from an average of 35 to 51 degrees in a patient with a normal isosecretory curve The number of experiments are insufficient to form any definite conclusions

Bastedo¹¹ concluded from the literature, chiefly from Crohn's work, that atropin has no useful clinical effect in any dosage, it does not lessen

6 Hecht, P Action of Atropin on Stomach, *Deutsch Arch f klin Med* **136** 296 (July) 1921

7 Keeton, R W, Luckhardt, A B, and Koch, F C Gastric Studies, *Am J Physiol* **51** 469 (April) 1920

8 Barclay, A E Alimentary Tract, 1915, p 17

9 Rehfuss, M E *Tr Am Gastro-Enterol Assn*, 1918, p 25

10 Crohn, B B Studies in Fractional Estimation of Gastric Contents, *Am J M Sc* **155** 801 (June) 1918

11 Bastedo, W A Points in the Pharmacology of Certain Drugs Used for Stomach Effects *Am J M Sc* **159** 53 1920

the digestive secretion, but if given in maximal dose hypodermically it lessens the interdigestive secretion and lessens pylorospasm. Bennett and Dodds¹² show one chart of the free hydrochloric acid curve before and after gastric lavage with 1/100 grain atropin in 100 c c water. The curve was about the same for one hour and then the one after atropin dropped to almost zero and remained low for two hours.

Because of the foregoing variance of views and the lack of sufficient convincing research on the clinical action of atropin on stomach function, it was decided to test its action, as measured by fractional gastric analysis, on a series of normal and pathologic stomachs. We have observed, as has Kopeloff,¹³ that the same person does not always respond with the same acidity, type of curve, or evacuation time, on different days even when using the same test meal and endeavoring to make all other factors equal. However, we do not consider that this variation is marked enough to influence greatly the final results in a study such as this, providing sufficient observations are made. In subjects accustomed to using the tube we have run two or more fractional curves on the same subject and found that there is a much greater tendency for a person to manifest one type of curve and about the same acidity and emptying time than there is for him to show marked variations.

Procedure—The subject, on a morning fasting stomach, swallowed the small fractional tube and the fasting contents were aspirated. An Ewald meal consisting of two slices of bread and 400 c c of water was then given, with the tube left in place, and from 5 to 10 c c of contents was aspirated every fifteen minutes. The emptying point was taken when the return was consistently free from bread. Several specimens were usually taken after this point was reached. There was noted on each specimen the percentage of solids and the presence or absence of bile or blood. The free and total acidity was determined by the Toepfer method. All subjects were accustomed to the use of the tube before the observations were made, and an effort was made to have them continue on about the same intake of food and water. The normal curve and the curve after the administration of the drug were all taken within a few days of each other.

Since emphasis has been laid on the dosage and method of administration a series of cases were taken, giving the drug in different dosage by mouth and hypodermically. Twenty-five observations have been made.

12 Bennett and Dodds. A Contribution to the Study of the Mechanism of Secretion in the Upper Alimentary Tract, *Internat J Gastro-Enterol* **1** 121 (Aug) 1921.

13 Kopeloff, N. Individual Variation as Influencing Rehfuess Fractional Method of Gastric Analysis, *J A M A* **78** 404 (Feb 11) 1921.

REPORT OF CASES

1 The effect of administration of $1/50$ grain atropin dissolved in 1 ounce water given given through the tube just previous to giving the Ewald meal

CASE 1—*Diagnosis*—Pyloric ulcer without obstruction The control test showed a hypersecretory type of curve with an average free hydrochloric acid of 58.2 degrees and total acidity 74 degrees over a period of two and three-quarters hours. The emptying time was two and a quarter hours. Two days later a curve was again made of this patient, after giving $1/50$ grain atropin in 1 ounce water through the tube just previous to the Ewald meal. The result shows the same type of curve reaching its height at the same time and practically the same average acidity. The emptying time remained the same. In Figure 1 are plotted the total acidity curves with and without atropin.

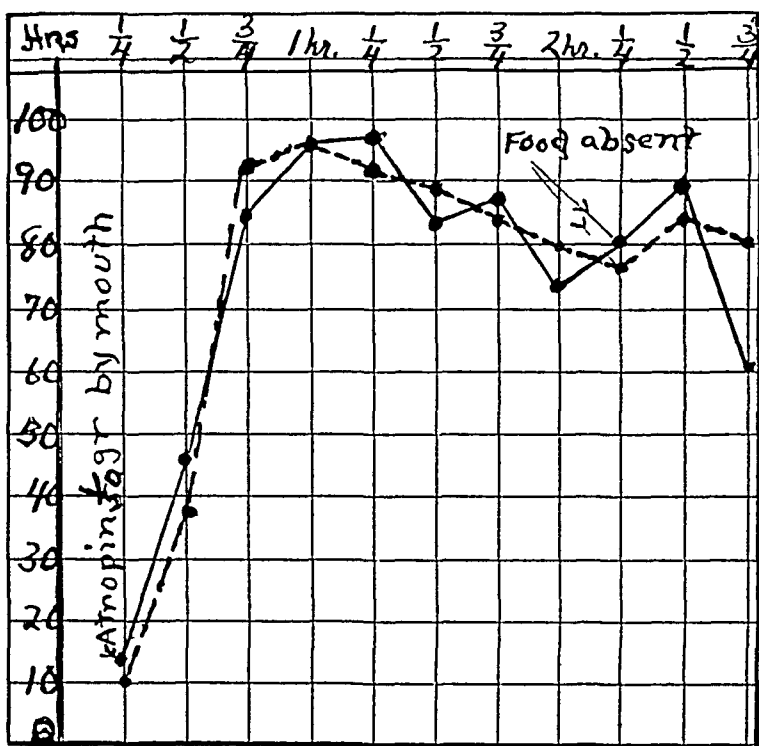


Fig 1—Total acidity curves with and without atropin in Case 1

CASE 2—*Diagnosis*—Prepyloric ulcer with moderate obstruction The control showed a hypersecretory curve with its peak at two hours, an average free hydrochloric acid of 58.2 degrees and an average total acidity of 66.7 degrees, with an emptying time of two and a quarter hours. After atropin, as given in the previous case, the same type of curve was obtained with its height at two hours, an average free hydrochloric acid of 47.3 degrees (10.9 degrees less than control), and an average total acidity of 80.4 degrees (13.7 degrees more than control). The emptying time was delayed from two and a quarter to three hours.

CASE 3—Normal subject The control test showed an iscretory curve with an average free hydrochloric acid of 32 degrees and total acidity of 59 degrees. After atropin, as previously given, the average free hydrochloric acid was 22 degrees (a reduction of 10 degrees), and an average total acidity of 45 degrees (a reduction of 14 degrees). The emptying time was delayed from one and a quarter hour in control to one and a half hours after atropin by mouth.

Table 1 shows a summary of these three cases in which 1/50 grains atropin was given by mouth just previous to the test meal. No marked effect is shown by the drug, although there is a tendency toward lowering of the acidity and a delay in evacuation time. What effect the drug may have had after more complete absorption cannot be stated, but it is evident that there is no or little direct local effect on the mucosa as maintained by Bennett and Dodds¹²

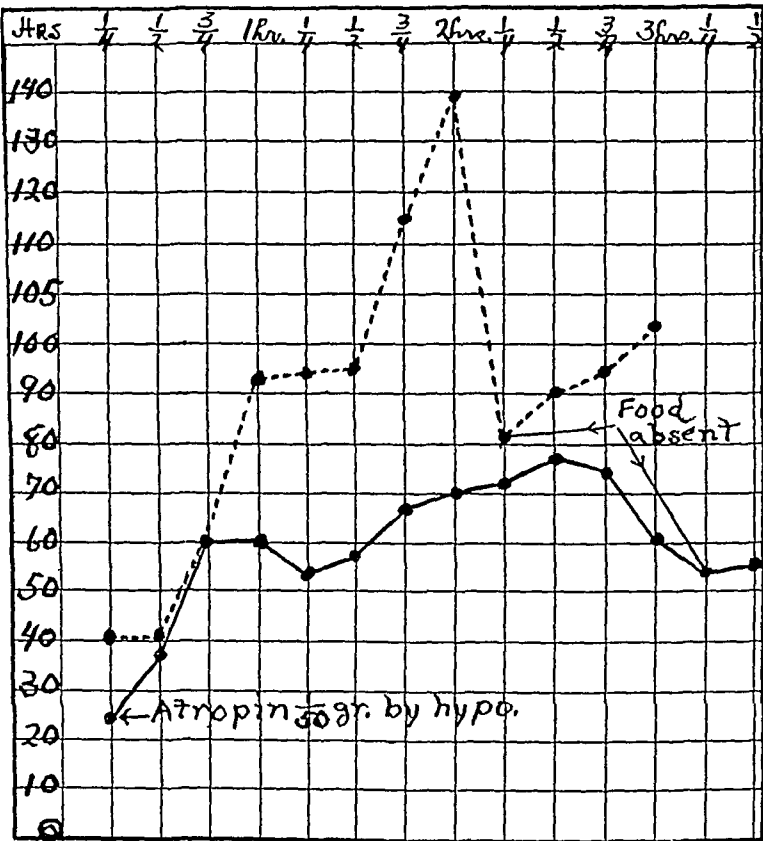


Fig 2—Total acidity curves in Case 4

2 The effect of administration of 1/50 grain atropin sulphate hypodermically just before meal

TABLE 1—THE EFFECT OF 1/50 GRAIN ATROPIN SULPHATE IN 1 OUNCE WATER GIVEN THROUGH TUBE JUST PREVIOUS TO EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time		Bile	
	Con- trol	Atro- pin	Con- trol	Atro- pin	Con- trol	Atro- pin	Con- trol	Atro- pin	Con- trol	Atro- pin	Con- trol	Atro- pin
M S	58.2	58.1	74.0	73.7	78	82	97	97	135	135	0	0
M H	58.2	47.3	66.7	80.4	105	65	140	105	135	180	0	+
H J	32.0	22.0	59.0	45.0	44.0	34.0	73.0	63.0	75	90	0	0
Average	49.4	42.4	66.5	66.3	75.6	75.6	103.3	89	115	135		

CASE 4—*Diagnosis*—Prepyloric ulcer with moderate obstruction After $\frac{1}{50}$ grain atropin was given hypodermically, the curve showed a lower trend than the test curve The curves of total acidity are seen in Figure 2 The average free hydrochloric acid was reduced 32.4 degrees, and the average total acidity was reduced 8.4 degrees The emptying time was delayed from two and a quarter to three and a quarter hours

CASE 5—*Diagnosis*—Duodenal ulcer A control curve showed a hypersecretory curve with a sharp rise at two and a half hours After $\frac{1}{50}$ grain atropin hypodermically, the curve started at the same level as in the control but showed a gradual descent without the sharp rise toward the end of digestion The average free hydrochloric acid was reduced 45.9 degrees, and average total acidity 3.6 degrees The emptying time was delayed one-quarter hour

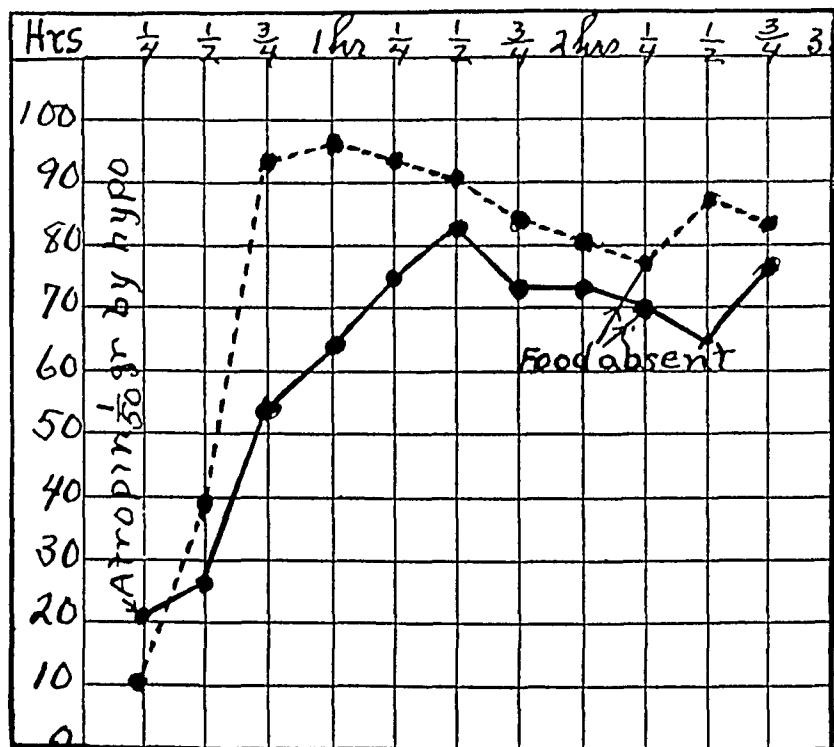


Fig 3—Total acidity curves in Case 6

CASE 6—The same patient as observed in Figure 1 After a hypodermic of $\frac{1}{50}$ grain atropin both free and total acidity showed a slight reduction 13.2 and 12.3 degrees, respectively The emptying time remained the same Figure 3 shows the total acidity curves

The tabulated results in these three cases are shown in Table 2

There is a moderate reduction of acidity in all cases with a slight prolongation of the emptying time

3 The effect of administration of $\frac{1}{50}$ grain atropin hypodermically one hour previous to the test meal These nine subjects were all considered to be free from organic or functional gastric disease The majority were in the psychopathic ward and suffered from mild dementia praecox or slight psychosis Table 3 gives our findings

In no case was the average free or total acidity as high after atropin as it was in the control curve carried out under identical condi-

tions In two cases, however, the free and total acidity went slightly higher at one point than in the control The evacuation time averaged practically the same with atropin as without it Figure 4 shows the curves of total acidity in a case demonstrating the average effect of $\frac{1}{50}$ grain atropin hypodermically given one hour previous to the Ewald meal

TABLE 2—THE EFFECT OF $\frac{1}{50}$ GRAIN ATROPIN SULPHATE GIVEN HYPODERMICALLY JUST PREVIOUS TO EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time		Bile	
	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro
	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin
A G	58.2	25.8	66.7	58.3	110.0	35	140	77	135	195	0	0
H H	85.8	39.9	96.0	60.0	95	58	113	113	105	120	+2	+4
M S	58.2	45.0	74.0	61.7	80	65	95	83	135	135	0	0
Average	67.4	36.9	78.9	60	91.6	52.6	116	91	125	145		

TABLE 3—THE EFFECT OF $\frac{1}{50}$ GRAIN ATROPIN SULPHATE HYPODERMICALLY ONE HOUR PREVIOUS TO EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time		Bile	
	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro
	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin
P S	33.3	28.6	42.8	41.8	50	35	60	44	120	120	0	0
A L	26.4	25.6	50.4	37.5	35	47	54	59	100	100	0	0
G S	36.0	8.8	54.1	17.6	60	13	80	21	80	120	0	+4
F M	22.0	4.0	29.4	18.0	40	10	50	35	100	140	0	0
J M	37.0	27.4	52.2	37.0	56	34	72	56	100	140	0	+1
A D	40.0	25.5	52.0	41.0	51	55	66	70	120	100	0	0
M B	43.3	24.8	49.5	35.6	78	46	83	60	120	120	0	0
P G	37.2	5.6	42.0	38.0	63	12	70	45	140	60	0	0
M K	42.6	15.0	62.3	56.5	67	16	77	60	80	40	0	0
Average	35.3	18.9	48.5	35.8	55.5	29.7	68	50	106	104		

4 Table 4 shows the results in one case of ulcer and in two normal persons from administering $\frac{1}{100}$ grain atropin hypodermically seven hours and again immediately before the test meal The results are similar to those obtained by giving $\frac{1}{50}$ grain hypodermically In all three cases there was a moderate reduction of acidity, while the emptying time remained virtually the same Figure 5 shows such a curve

TABLE 4—THE EFFECT OF $\frac{1}{100}$ GRAIN ATROPIN SULPHATE HYPODERMICALLY SEVEN HOURS AND AGAIN JUST PREVIOUS TO EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time		Bile	
	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro	Con	Atro
	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin	trol	pin
M S	85.8	65.8	96.0	85.7	94	90	112	90	105	120	0	+1
C L	40	30	62	51	80	73	96	84	120	130	0	0
H B	32.0	23	59	42.5	43	40	73	58	75	75	0	0
Average	52.6	39.6	72.3	59.7	72.3	67.6	93.7	77.8	100	108		

5 Three patients with extra-abdominal conditions, who were accustomed to the tube, were tested as to the action of continuous administration of tincture of belladonna. One c c was given four times daily for three days. These patients all exhibited symptoms of bella-

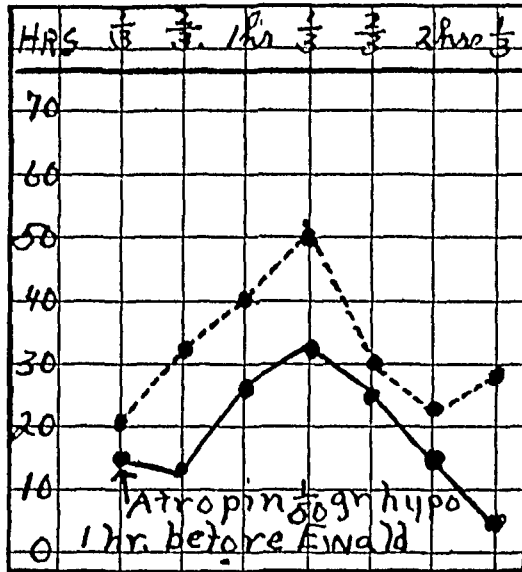


Fig 4—Total acidity curves in a case showing average effect of atropin

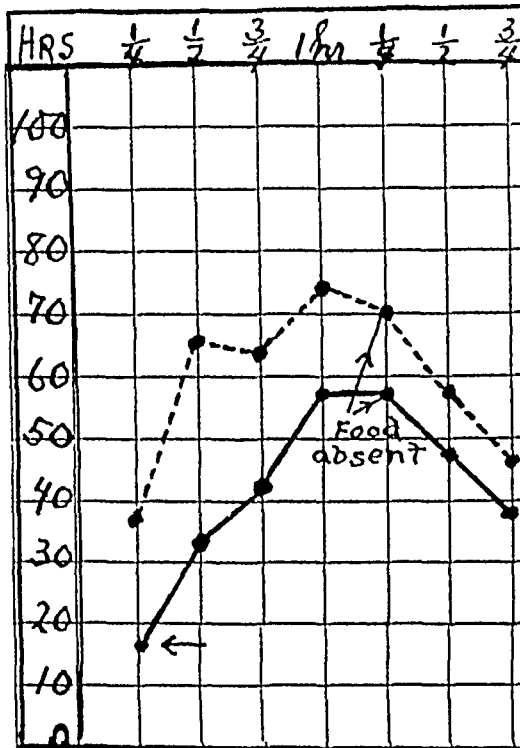


Fig 5—Moderate reduction of acidity with emptying time unchanged

donna action in moderate degree. The results are shown in Table 5. There is a moderate reduction of acidity in all cases. A control curve with one demonstrating the effect from such an administration of belladonna is shown in Figure 6.

TABLE 5—THE EFFECT OF REPEATED ADMINISTRATION OF TINCTURE OF BELLADONNA BY MOUTH TO A POINT OF TOLERANCE

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time		Bile	
	Control	Atro-pin	Control	Atro-pin	Control	Atro-pin	Control	Atro-pin	Control	Atro-pin	Control	Atro-pin
R B	34.1	22.0	60.1	36.5	47	37	72	54	75	75	0	0
H C	61.5	30.0	76.7	51.0	80	47	98	68	90	105	0	0
B V	32.6	29.4	43.4	40.7	49	38	61	48	120	135	0	0
Average	42.7	27.1	60	42.4	58.6	40.6	77	56.6	95	105		

6 Inasmuch as the chief clinical use of an acid reducing drug lies in the control of acidity in ulcer management, observations were made on a patient while on frequent cream feeding (Ulcer management)

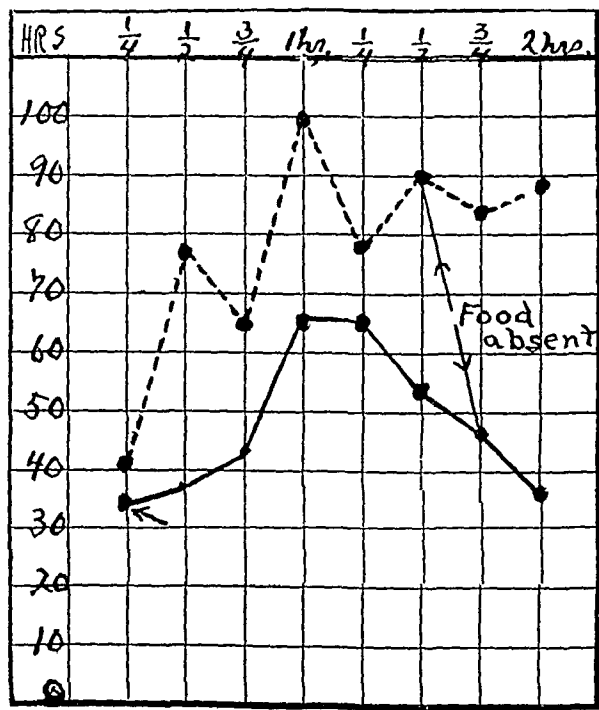


Fig 6—Control curve and curve showing effect of belladonna. Arrow points to time after taking 1 c c tincture of belladonna four times daily for three days

These were all made on the same patient, whose case had been diagnosed and was later operatively proved to be a prepyloric ulcer with moderate obstruction

After the first morning feeding of 3 ounces cream, the average free acidity for the following two hours was 93.7 degrees. Atropin 1/50 grains dissolved in 1/2 ounce of water given through the tube and was followed immediately by 3 ounces cream swallowed around the tube. The free hydrochloric acid, during the next two hour period, averaged 78.3 degrees. The same dose of atropin and cream was again given, and during the next one and one-half hours the average free

hydrochloric acid was 65.5 degrees, a reduction of 28.2 degrees under the first period after cream only. After an interval of two days, this same patient was again observed. The first period of two hours after cream showed an average free hydrochloric acid of 76.9 degrees. Three ounces cream was again given, together with $\frac{1}{100}$ grain atropin hypodermically, and the next two hours showed an average free hydrochloric acid of 63.5 degrees. Cream and atropin were again given, and the next two hour period showed an average of 31.2 degrees. Cream only was then given and the following hour showed an average of 87 degrees.

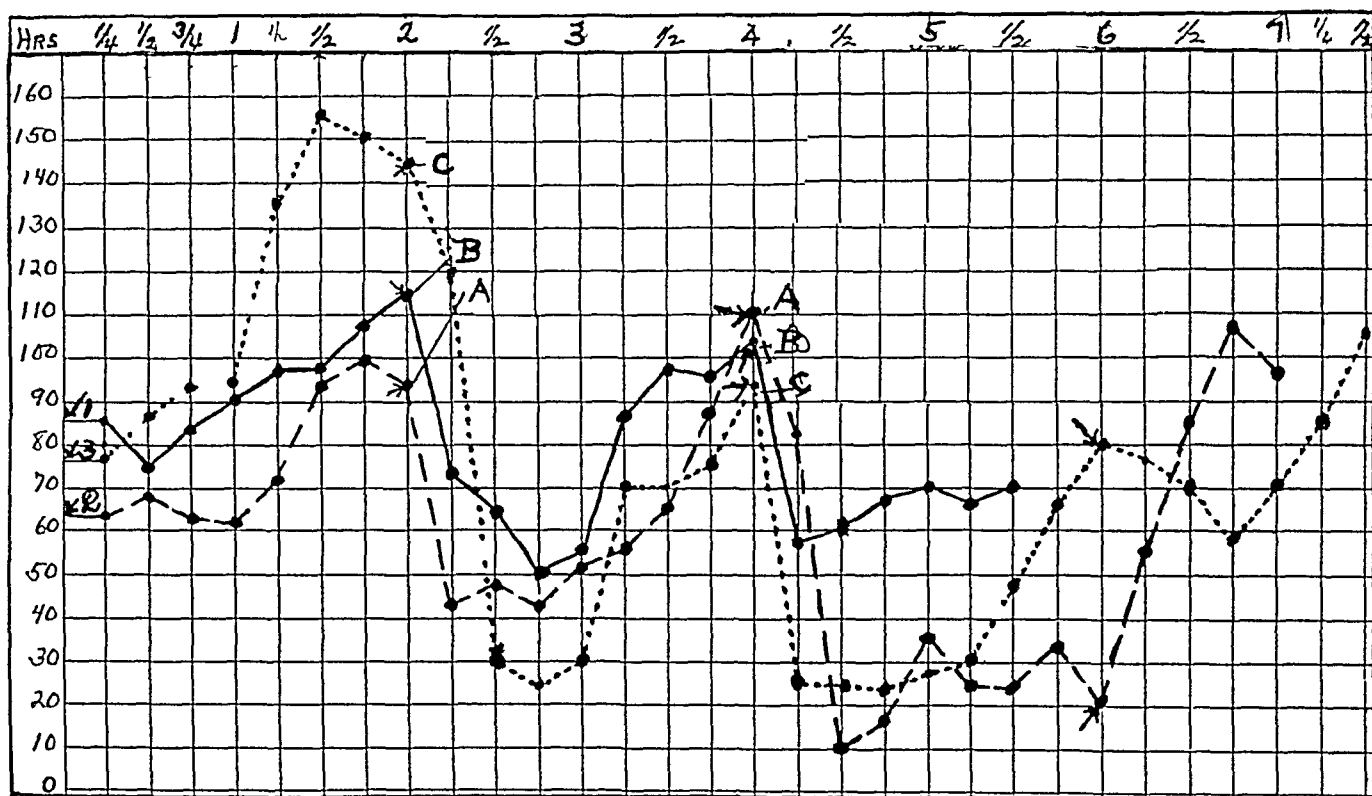


Fig 7—Three curves of the free acid on the same patient taken on alternate days. The first two-hour period in each instance is after taking 3 ounces of 10 per cent cream, the second, after taking cream and atropin, the third, after taking cream and atropin, and the fourth after taking cream only. Arrows indicate the administration of 3 ounces of 10 per cent cream. A, $\frac{1}{100}$ grain atropin hypodermically, B, $\frac{1}{50}$ grain atropin by mouth, C, $\frac{1}{50}$ grain atropin hypodermically.

After an interval of two days the same procedure was again carried out, except that $\frac{1}{50}$ grain atropin was given hypodermically. The first period of two hours after 3 ounces cream gave an average free hydrochloric acid of 116.6 degrees, cream and a hypodermic of $\frac{1}{50}$ grain atropin was then given and the following period showed an average free hydrochloric acid of 64.1 degrees. Cream and atropin was again given and the period following showed an average of 40.6 degrees. Cream alone was then given, and during the following one

and one-half hours the average was 77.7 degrees, yet the patient was complaining of a very dry throat and had dilated pupils. These curves just described are shown in Figure 7.

DISCUSSION

From the foregoing experiments a fairly accurate and concrete picture is obtained of the clinical action of atropin on the stomach. It seems evident that there is a secretory and motor depressing action in direct relation to the dose given, yet on the other hand, using doses compatible with safety it is impossible to demonstrate the marked action seen on lower animals. This may be due to a different pharmacologic action.

In three cases the local application of $\frac{1}{50}$ grain atropin in 1 ounce of water to the fasting stomach mucosa made no marked change in the secretory curve after an Ewald meal, except that the high point of free and total acidity was slightly lowered in two cases, in which also the emptying time was slightly delayed. This seems to prove that there is little or no direct local action on the mucosa, as assumed by Bennett and Dodds, but that the effect comes only after absorption.

In eighteen cases the effect on the secretory curve after an Ewald meal was noted from administration of maximal clinical doses either hypodermically or continuous dosage. The average free acidity was reduced 32 per cent and the average total acidity 27 per cent. In no case was the average free or total acidity higher with atropin than without it. This reduction effect seemed more pronounced in lowering the high point of the curve, although in two cases both the free and total acidity rose to a higher point after atropin than had occurred in the test curve.

The average emptying time was delayed ten minutes, although three cases showed a more rapid evacuation after atropin. These cases occurred in the series which received a hypodermic of $\frac{1}{50}$ grain atropin an hour previous to the meal, and may have been due to greater relaxation of the pylorus.

CONCLUSIONS

- 1 The effect of atropin on the human stomach is to depress both the secretion and motor action, but is much less than that observed on lower animals.

- 2 Maximal clinical dosage of atropin depresses both the free and total gastric acidity about 30 per cent.

- 3 The same dosage lessens motor movements in the human stomach enough to delay the evacuation time after an Ewald meal about ten minutes. Bile is more frequently observed after atropin, probably due to greater relaxation of the pylorus.

THE ANEMIA OF CHRONIC NEPHRITIS^{*}

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Anemia is commonly observed in nephritis. It may be so severe that the question arises as to whether the anemia is the primary disease.

Various causes of the anemia of nephritis have been suggested, but comprehensive or conclusive studies have not been made. Grawitz¹ maintains that decrease in the blood elements does not take place if cardiac efficiency is maintained. He recognizes two groups of cases of chronic nephritis: (1) those with efficient cardiac function and adequate peripheral circulation, and (2) those with deficient cardiac function and circulatory stasis. In this latter group, either dilution or concentration of the blood plasma takes place. If the plasma is diluted a relative or dilution anemia occurs. Hamelin² has noted the association of anemia and uremia. He emphasizes the importance of hydremia and of hemotoxic substances in the blood as possible etiologic factors. Ceconi³ did not find decrease in resistance of the erythrocytes in nephritis. He concludes that the anemia of chronic nephritis is due to the inhibiting effects of urinary poisons on hematopoiesis. He also observed that the fragility of the erythrocytes bears no specific relationship to the toxicity of the blood serum in nephritis. Da Costa⁴ recorded the occurrence of a moderate decrease of hemoglobin and erythrocytes in chronic parenchymatous nephritis, and says, that, exceptionally, this may become extreme. He believes that the anemia, loss of albumin through the kidneys, and diseases in other organs are related. Grignani⁵ believes that some substance which is toxic to the bone marrow is produced and that defective diet and hydremia play some part in the condition.

The material used in this study consists of 187 cases diagnosed chronic glomerular nephritis⁶ at the Mayo Clinic from July 1, 1919, to Aug 1, 1921, and other pathologic cases selected at random. Cases of chronic nephritis complicated by diseases in the kidney or other

* From the Section on Clinical Investigation, Division of Medicine, Mayo Clinic

1 Grawitz, E. *Klinische Pathologie des Blutes*, Leipzig, Thieme, 4 1011, 1911

2 Hamelin, A. *Contribution a l'etude de l'anemie urémique*. Paris, 1904

3 Ceconi, A. *Le Resistenze Globulari Nella Nefrite*, *Clin Med ital* 44 15, 1905

4 DaCosta, J. C. *Clinical Hematology*, Philadelphia, Blakiston's, 1920, p 474

5 Grignani, R. *Il Ricambio Emoglobinico Nei Nefritici. Contributo Allo Studio della Pathogenesi dell 'Anemia dei Nefritici*, *Arch di path e clin med* 1 48, 1921

6 Volhard and Fahr classification

organs, such as pyelonephritis, hydronephrosis, tuberculosis, malignancy, and so forth, and all cases of hemorrhage were excluded. One hundred and five cases of the 187 showed anemia, which might correctly be designated as the anemia of chronic nephritis, and eighty-two were without anemia.⁷

ETIOLOGY

Etiologically three types of anemia are recognized (1) anemia secondary to acute or chronic loss of blood, (2) anemia secondary to excessive hemolysis, and (3) anemia secondary to faulty or deficient hematopoiesis.

Hemorrhage—Probably hemorrhage may play some part in the cause of the anemia of acute nephritis, but in the group of cases herein designated as anemia of chronic nephritis all cases exhibiting macroscopic loss of blood were excluded. Long continued microscopic loss of blood in the urine and stools was investigated in order to ascertain its importance. The blood in the urine is indicated on a basis of 1, 2, 3 and 4. If the amount of blood in the urine is designated as Grade 4, blood is present macroscopically and the case is, therefore, excluded from this study.

Experiments to show the approximate amount of blood present in the urine daily in cases of chronic blood loss indicate that approximately from 0.5 to 1.5 cc of blood for each liter of urine is lost, an amount probably insufficient to produce anemia. Examinations of stools were made daily for occult blood and all cases showing macroscopic blood were excluded. The incidence of positive tests for occult blood was so small as to be negligible. Table 1 shows the average amount of blood in the urine in eighty-nine cases of anemia of nephritis, selected at random from the 105.⁸ In thirty-four cases (38 per cent) the urine did not contain blood cells. It will be seen that no relationship exists between the microscopic amounts of blood in the urine and the anemia.

Excessive Hemolysis—A hemolytic basis of the anemia deserves special consideration. The common occurrence of vascular injury, and the hemorrhagic tendency in many cases of chronic nephritis suggests that hemolysis may play some part in this connection as may changes

⁷ In this classification patients were designated anemic whose hemoglobin values were below 70 per cent on the Dare instrument and with erythrocyte counts less than 4,000,000. The values with the Dare instrument approximate those obtained with the Haldane-Palmer Method when the values are 70 per cent or lower (Fig 1), the curves for each are practically parallel to this point. Because the earlier estimations of hemoglobin were made with a Dare instrument, the subsequent estimations were made on this instrument for purposes of comparison.

⁸ These calculations do not take into consideration the red blood cells destroyed by hemolysis.

in the coagulative substances of the blood Leopold,⁹ McKee,¹⁰ and Ponder¹¹ have investigated the presence of hemolytic substances in the urine of human beings and have proved their existence in health and in various diseases This hemolytic action is not due to osmosis but probably to bile acids, as Ponder has pointed out (Leopold induced uranum nephritis in animals and found hemolytic substances in the urine Our results correspond closely to those of Leopold)

In order to ascertain the presence of hemolytic substances in the urine, eighty-two patients, selected at random, coming for examination during 1921, were divided into three groups Group 1, fifty-two normal and nonnephritic patients Group 2, eighteen patients with chronic nephritis without anemia, and Group 3, twelve patients with chronic nephritis and anemia The following method was employed

The erythrocytes washed with physiologic solution of sodium chlorid three times were suspended in this solution (1:100) Six tubes were set up containing erythrocyte suspension and freshly voided urine

TABLE 1—BLOOD IN THE URINE IN EIGHTY-NINE CASES OF ANEMIA OF NEPHRITIS

Cases	Blood in Urine, Grade	Hemoglobin, Average per Cent	Erythrocytes, Average Count, Millions
34	0	59.0	3.01
39	1	54.7	3.31
12	2	58.0	3.65
4	3	57.0	2.95

in the following proportion Tube 1, 1:100 erythrocyte suspension, 1 c c, and urine, 0; Tube 2, suspension, 1 c c, and urine, 1 c c; Tube 3, suspension, 1 c c and urine, 0.75 c c; Tube 4, suspension, 1 c c, and urine, 0.5 c c; Tube 5, suspension, 1 c c and urine, 0.25 c c; Tube 6, suspension, 1 c c and urine, 0.1 c c

After incubation for three hours at 37 C, the tube showing complete hemolysis indicated roughly the amount of hemolytic substance in the urine

The results in Group 1 were positive 25.5 per cent and negative 74.5 per cent, in Group 2, positive 65 per cent and negative 35 per cent, in Group 3, positive 34 per cent, and negative 66 per cent Specimens of urine of patients with chronic nephritis (Group 3) were examined from day to day, during the development of the anemia Hemolysins did not increase in the urine These experiments indicate that hemolytic

9 Leopold, E. J. Ueber die Hamolyse bei Nephritis, *Ztschr. f. klin. Med.* 60:480, 1906

10 McKee, C. S. On the Hemolytic Action of the Urine in Certain Conditions, *Brit. M. J.* 2:596, 1915

11 Ponder, E. The Presence of Hemolytic Substances in Human Urine, *Brit. J. Exper. Path.* 2:34, 1921

substances are present in the urine in normal and in pathologic conditions, and that in the cases of chronic nephritis without anemia they are present in greater amounts than in chronic nephritis with anemia. The findings in anemia of nephritis and in normal conditions lead to the conclusion that these substances in the urine do not have a bearing on the production or maintenance of the anemia of chronic nephritis.

Hemolytic substances are rarely present in the blood serum of chronic nephritis. Grafe and Graham,¹² reported a case of chronic nephritis in which the blood serum intermittently showed hemolytic substances. Many attempts have been made to demonstrate the presence of hemolytic substances in the blood serum in hemolytic anemia, but without success. Noguchi¹³ showed that normal serum has anti-hemolytic properties toward sodium oleate. Much and Holzmann,¹⁴ studying the action of the fresh serum of human beings on the hemolysin of cobra venom, proved that the serum of patients with certain mental diseases had a marked antihemolytic action. Clark and Evans,¹⁵ using sodium oleate as a hemolytic agent and guinea-pig corpuscles, have demonstrated a definite decrease in the protective property of serums of patients with pernicious anemia. In other cases, both normal and pathologic, there was a remarkable constancy in the protective power of the serum. In order to ascertain the status of serum of patients with nephritis and anemia with regard to hemolysis, the following technic was used:

Distilled water (from Pyrex glass flasks) was the hemolytic agent. Racks with a double row of sixteen small Wassermann tubes were set up similar to the technic of Giffin and Sanford.¹⁶ In the first tube in each row at the left was put 0.92 c c of 5 per cent salt solution, in the second tube, 0.88 c c, and so on, each tube containing 0.4 c c less of the salt solution than the tube to the left. In the first tube was placed 0.08 c c of redistilled water, in the second tube 0.12 c c, and so on, each tube containing 0.04 c c more of redistilled water than the tube to the left. The final dilutions were: Tube 1, 0.46 per cent of salt; Tube 2, 0.44 per cent; Tube 3, 0.42 per cent; and Tube 16, 0.16 per cent. The total volume in each tube was 1 c c. Volumetric pipets were used in all measurements. The salt solution was made up with extreme care every

12 Grafe, E., and Graham, A. L. Untersuchungen über Isolyse, München med Wchnschr **58** 2257, 1911.

13 Noguchi, H. Ueber gewisse chemische Komplementsubstanzen, Biochem Ztschr **6** 327, 1917.

14 Much, H., and Holzmann, W. Eine Reaktion im Blute von Geisteskranken, München med Wchnschr **56** 1001, 1909.

15 Clark, H. M., and Evans, F. A. One Factor in the Mechanism of Hemolysis in Hemolytic Anemia, Bull Johns Hopkins Hosp **31** 354, 1920.

16 Giffin, H. Z., and Sanford, A. H. Clinical Observations Concerning the Fragility of Erythrocytes, J Lab & Clin M **4** 465, 1919.

six days and checked against the discarded solution. Pipets did not come in contact with the stock salt solution, enough for the day's needs was taken out of the bottle each day.

Blood was obtained by venipuncture, 2 c c was placed in a test tube containing 2 mg potassium oxalate and 4 c c in a centrifuge tube was allowed to clot and then centrifuged for fifteen minutes. One-tenth of a cubic centimeter of the fresh serum thus obtained was placed in each tube of the second row and the tubes were shaken gently, 0.02 c c of oxalated blood¹⁷ was added to each tube, the tubes were again shaken gently and allowed to stand two hours at room temperature.

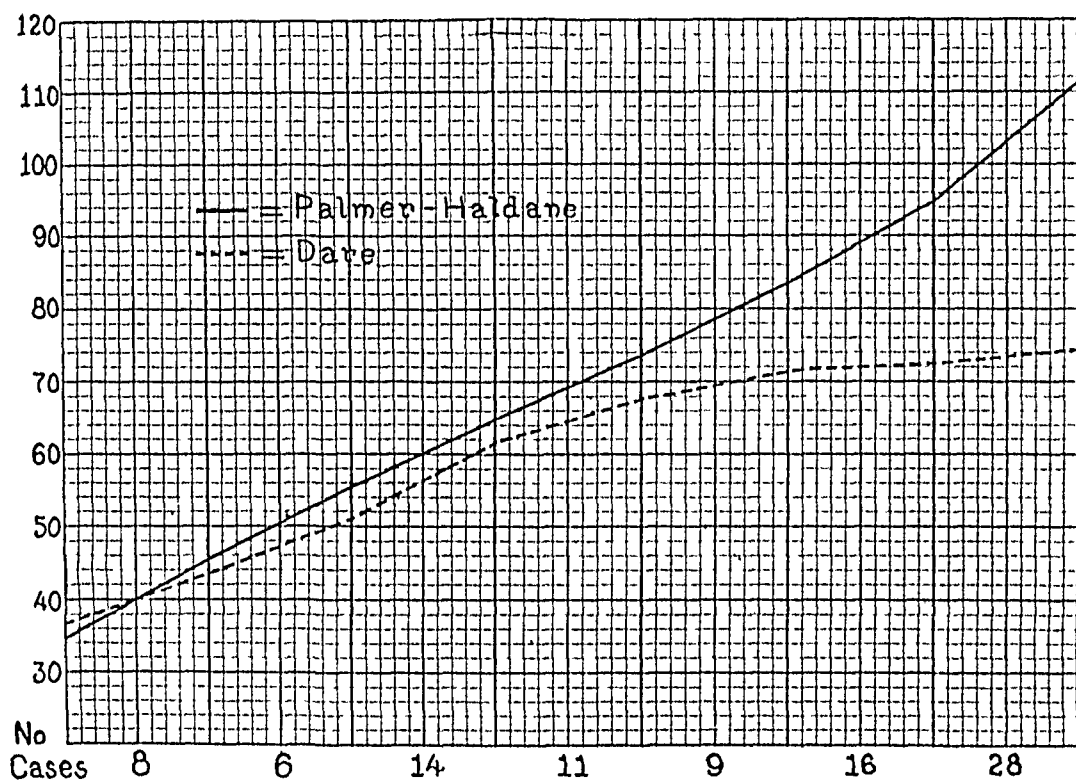


Fig 1—Comparative hemoglobin values obtained with the Haldane-Palmer method and the Dare hemoglobinometer

The readings of beginning and complete hemolysis in the tubes of the first row indicate the fragility range of the red blood cells to hypotonic salt solution. In the tubes showing beginning hemolysis, the supernatant fluid shows a faint trace of the dissolved hemoglobin. Complete hemolysis is indicated by the absence of red blood cells in the bottom of the tube and the clear red transparent solution. The tubes showing beginning and complete hemolysis are compared in first and second rows. The difference in the per cent of hypotonic salt solution

¹⁷ If the erythrocyte count was 4,000,000 or more, the amount of oxalated blood used was 0.02 c c, if from 2,000,000 to 4,000,000, 0.03 c c, and if under 2,000,000, 0.04 c c.

necessary to cause beginning and complete hemolysis indicates the degree of antihemolytic property of the serum examined. In Table 2 and in Figure 2 will be seen the average protection afforded by the blood serum in five types of cases: normal, pathologic condition other than nephritis without anemia, secondary anemia, anemia of chronic nephritis, and chronic nephritis without anemia.

A comparison of the five groups demonstrates that the serum exerts definite protection against hemolysis by hypotonic salt solution for red

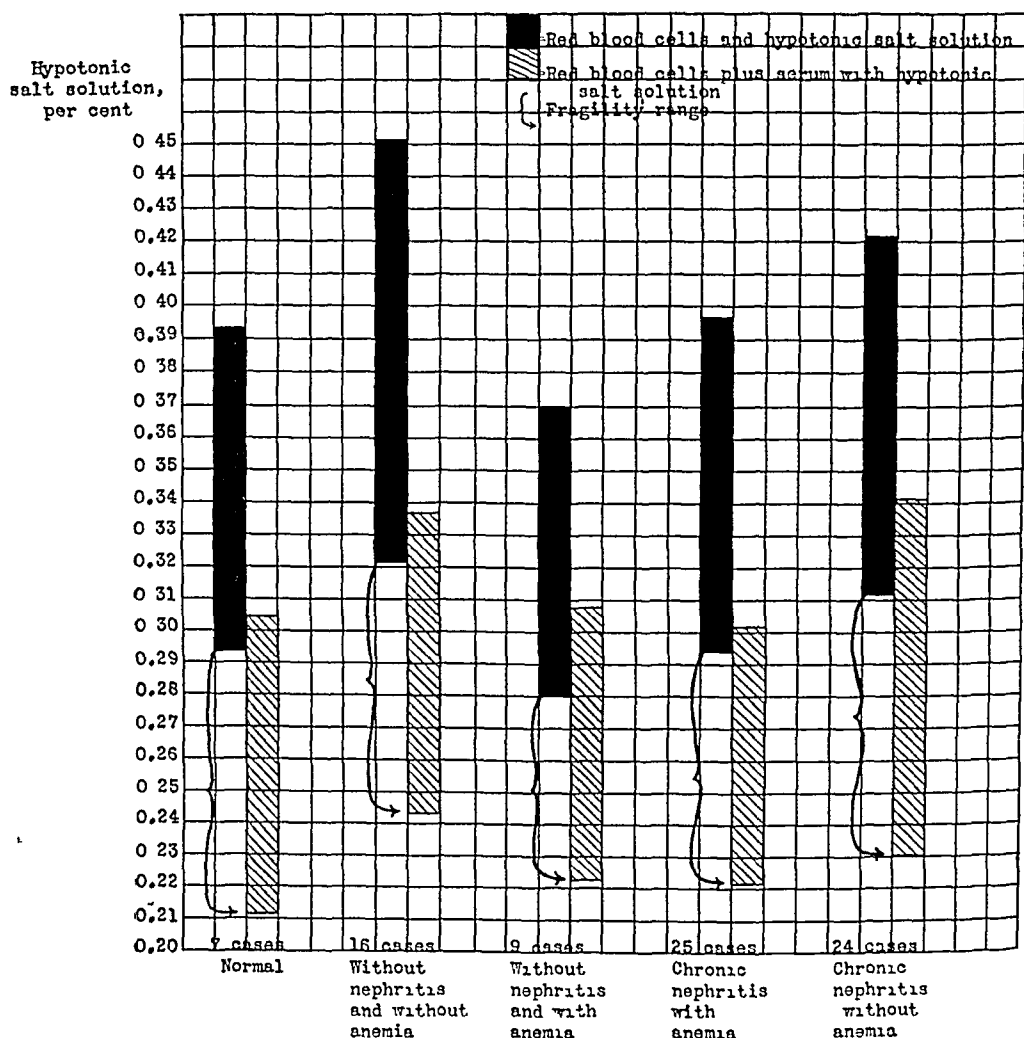


Fig 2—The average protection afforded by the blood serum against hemolysis by hypotonic salt solution in five types of cases

blood cells. This property of serum seems to be fairly constant, except for the anemias of the hemolytic type as has been shown by Clark and Evans. In the anemia of chronic nephritis serum does not show definite decrease in antihemolytic power. In two cases of uremia, a few days before death, the serum exhibited marked antihemolytic properties which increased until death. In cases of chronic nephritis in which the

blood serum was tested daily change was not noticed during the development of anemia

The results of this study would indicate that the anemia of chronic nephritis is not concerned with lack of protective power of the serum. Studies of the nature of this protective property of serum would indicate that the action depended on the colloidal property of the serum. Conditions which upset or disturbed the colloidal mechanism also produced changes in this protective action, heating, freezing, and shaking of the serum produced diminution of this action. After dialysis of the serum the dialysate and the residue both showed loss of this property. The dialysate and the residue were evaporated to their original volume to maintain the original salt concentration. The membrane did not show protective action. These findings also correspond to the conclusions reached by Clark and Evans.

It has been shown by Eppinger¹⁸ that excessive hemolysis usually occurs when the bile contains abnormally large amounts of urobilin and

TABLE 2—ANTHEMOLYTIC PROPERTY OF SERUM

Type	Cases	Average Protection Against Hemolysis, per Cent Less Salt
Normal	7	0.083
Without nephritis and anemia	16	0.077
Without nephritis but with anemia *	9	0.058
Chronic nephritis with anemia	25	0.07
Chronic nephritis without anemia	24	0.08

* Three cases of primary anemia are included

urobilinogen. Quantitative examination of the duodenal contents, as utilized by Schneider¹⁹ in the hemolytic anemias, shows large amounts of urobilin and urobilinogen. Giffin, Sanford, and Szlapka²⁰ have shown that average values for urobilin and urobilinogen in hemolytic jaundice are 2,050 and 1,100 units, respectively. In cases of pernicious anemia the average value for urobilin was 1856.5 and for urobilinogen 1604.5 units. Table 3 gives average values obtained in cases of anemia of nephritis: 600 units of urobilin and absence of urobilinogen in all cases except one. These findings correspond to those ordinarily found in secondary anemia.

18 Eppinger, H. Zur Pathologie der Milzfunktion, Berl. klin. Wchnschr. **1** 1509-1572-2409, 1913.

19 Schneider, J. P. The Hematopoietic-Hemolytic Index: a Proposed Determination Helpful in the Differential Diagnosis of Types of Pernicious Anemia Amenable to Cure by Splenectomy, Jour. Lancet **37** 105, 1917, Further Quantitative Study of the Duodenal Blood Derived Pigments, Arch. Int. Med. **19** 156 (Feb.) 1917.

20 Giffin, H. Z., Sanford, A. H., and Szlapka, T. L. The Estimation of Urobilin and Urobilinogen in the Duodenal Contents, Am. J. M. Sc. **155** 562, 1918.

Hemolysis occurs constantly in the body, but there is no exact method of determining the normal rate of hemolysis. However, in the hemolytic anemias in which hemolysis is excessive, its recognition by clinical and laboratory means is usually possible. Such means, as applied in this study, have indicated that blood is not excessively destroyed in the anemia of chronic nephritis.

Defective blood formation is probably the important factor in the cause and maintenance of the anemia of chronic nephritis. This premise is supported by lack of evidence of abnormal blood destruction and

TABLE 3—FINDINGS IN CHRONIC NEPHRITIS WITH ANEMIA

Leuko cy tes												Duodenal Contents	
Cases	Hemo- globin, per Cent	Erythrocytes			Num- ber	Poly- morpho nuclears, per Cent	Small Lympho cytes, per Cent	Large Mono- nuclears, per Cent	Eosino- phils, per Cent	Baso phils, per Cent	Uro billin ogen, Units	Uro billin, Units	
		Mil lions	Re- ticu- lated	Nu- cle ated									
A354932	39	2 31		0	7,400	64 5	24 5	10 5	3 5	0 5	0	400	
A359322	68	3 74	0 2	0	7,400	60 0	30 0	4 0	3 5	2 5	200	600	
A334085	42	2 69	0 3	0	7,700	71 0	19 0	8 5	3 0		0	200	
A371812	62	4 05	1 3	0	12,000	58 8	33 5	5 0	1 5	1 5	0	400	
A361797	53	3 20	0 2	0	4,530	55 0	38 7	4 2	1 0	1 0	0	600	
A130794	44	2 52	0 1	1 cell	8,200	63 5	29 5	4 0	2 5	0 5	0	1,000	
A123990	60	3 43		0	6,800	59 0	33 0	2 0	4 5	1 5	0	600	
A374848	56	3 31	1 7	0	5,200	67 5	26 0	4 0	2 0	0 5	0	800	
A364350	54	3 02	0 3	0	8 400	70 0	23 5	3 5	2 5	0 5			
A380765	67	3 66	1 5		13 800	87 0	11 5		1 5		0	1,000	
A384638	42	2 30	0 4	0	5 700	80 5	14 5	2 5	2 0	0 5	0	600	

TABLE 4—BLOOD COUNTS IN CHRONIC NEPHRITIS

	Hemo- globin, per Cent	Erythro- cytes, Millions	Leuko- cytes	Color Index, per Cent	Poly- morpho- nuclear Leukocytes, per Cent	Lym- pho- cytes, per Cent	Large Mono- nuclear Leukocytes, per Cent	Eosino- phils, per Cent	Baso- phils, per Cent
Chronic nephritis with anemia (105 cases)	56	3.31	9,020	0.8+	69.1*	23.6	4.8	1.9	0.3
Chronic nephritis without anemia (79 cases)†	75	4.22	8,160	?	63.6*	26.5	6.3	3.4	0.4

* Differential counts are the average of thirty four cases

† In three cases blood counts were not recorded

by the fact that the blood picture of anemia of chronic nephritis corresponds to that of simple chronic anemia.

The erythrocytes of stained smears of the blood in cases of anemia of nephritis usually are moderately reduced in size, marked variation in the size is rarely noted. Poikilocytosis is rare, and achromia is usually mild. The incidence of reticulated red blood cells and of polychromatophilia is markedly low. Table 3 gives the average blood findings in eleven cases of the 105 in which the anemia of nephritis was severe. The low percentage of nucleated red cells and reticulated cells points to lack of action or sluggish action of regeneration by the bone marrow. Table 4 gives the average blood findings of two groups

of cases, 105 of chronic nephritis with anemia and seventy-nine without anemia. The average hemoglobin in the group with anemia was 56 per cent, which corresponds closely to the finding of DaCosta. No essential difference was noted in the leukocyte count in the two groups. In patients with anemia the per cent of polymorphonuclear leukocytes averaged 56 higher and the lymphocytes 28 lower than in patients without anemia.

The platelet count in eight cases of chronic nephritis with severe anemia averaged 152,000, a condition which may have some bearing on the hemorrhagic tendency in some of the more severe cases of chronic nephritis with anemia.

As will be shown, the rate of development of the anemia, its lack of response to therapeutic measures, transfusion, arsenic, and iron, bear out this conclusion of defective hematopoiesis. When the anemia has been maintained for a considerable period, the bone marrow seems to establish a constant low threshold of activity for the individual. In this group of anemias of nephritis, cases were studied in which the bone marrow functioned fairly satisfactorily at from 40 to 50 per cent of its normal activity level. Benzene produces a somewhat similar type of anemia. Minot²¹ described a case observed for three years, in which a satisfactory functioning level for the bone marrow was maintained at 80 per cent of normal. In the more severe types of nephritic anemia, some of the features of an aplastic type are more in evidence, that is, absolute lack of response to treatment, and complete absence of immature and regenerative types of red cells. This group can be designated as secondary aplastic anemias of chronic nephritis.

INADEQUATE HEMATOPOIESIS

It is obviously impossible in this paper to attempt to review the causes of defective formation of blood, for the great majority of anemias are concerned with defective blood formation. The anemias of malignant disease, chronic sepsis, and other chronic pathologic processes concern the hematopoietic system directly, little is known regarding the mechanism involved. The bone marrow suffers in certain metabolic diseases, such as myxedema, in which the blood picture is often extremely confusing. Poor hygienic condition is the cause of mild anemia, although the pallor of the skin in this type may not indicate an actual decrease of blood elements.

In any chronic disease in which alteration of the blood picture is so common as in chronic nephritis, the question of defective diet deserves consideration. Patients with this disease often have been underfed

²¹ Minot, G. R. *Clinical Discussion of the Anemias*, Oxford Med. 2: 589, 1920.

qualitatively and quantitatively for long periods. The chronic loss of albumin through the urine constitutes a loss of nitrogen to the organism, and its possible bearing on the production of anemia has been suggested. The retention of water in the blood and tissue have been made the explanation for the anemia of chronic nephritis. Not sufficient evidence is available to prove that hydremia or loss of albumin can cause a definite anemia.

The presence of a toxin or toxic agent in chronic nephritis has been assumed in order to explain the multiple tissue injury. As to whether this toxin is a known substance, and as the result of the renal damage appears in the blood in amounts sufficiently increased to cause injury to the bone marrow has never been proved. The possibility that this unknown agent, a hypothetic toxin, damages the bone marrow concomitantly with other vascular tissue must be considered.

Defective Diet—The majority of cases of chronic nephritis are recognized, and in lieu of more specific treatment a dietary regime is instituted involving considerable restrictions. The following warrant consideration relative to blood changes: (1) the effects of fasting, (2) a prolonged low caloric diet, and (3) a prolonged low protein diet. A large volume of clinical and experimental evidence is available to help decide this question of the results of defective diet on the blood. Heidenhain,²² Panum²³ and Voit²⁴ have shown that loss of body weight and decrease of blood in fasting animals are proportional, normal values thus being maintained for hemoglobin and erythrocytes. Ash²⁵ has shown that, in general, the blood is distinctly resistant to the effects of inanition. Complete abstinence from food for long periods, at least thirty-one days, does not cause deleterious effects on the blood. There is slight actual loss of hemoglobin, more marked during the second ten days. Fasting does not cause any striking loss of hemoglobin and erythrocytes from the blood.

Blood changes in low diets have been studied by von Hosslin.²⁶ The studies of Benedict²⁷ and his collaborators revealed slight changes

22 Heidenhain, R. P. H. *Disquisitiones Criticae et Experimentales de Sanguinis Quantitate in Mammalium Corpore Exstantis*. Halis, Gebauerio-Schwetschkianis, 1857. Quoted by Grawitz.

23 Panum, P. L. *Experimentelle Untersuchungen über die Veränderungen der Mengenverhältnisse des Blutes und seiner Bestandtheile durch die Inanition*, Arch f path Anat u Physiol **29** 241, 1864.

24 Voit, C. *Ueber die Verschiedenheit der Eiweisszersetzung beim Hungern*, Ztschr f Biol **2** 307 1866. Voit, C. *Gewichte der Organe eines wohlgenährten und eines hungernden Hundes*, Ztschr f Biol **12** 510, 1893.

25 Ash, J. E. *The Blood in Inanition*, Arch Int Med **14** 8 (July) 1914.

26 von Hosslin, H. *Ueber den Einfluss ungenügender Ernährung auf die Beschaffenheit des Blutes*, München med Wchnschr **37** 654-673, 1890.

27 Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M. *Human Vitality and Efficiency under Prolonged Restricted Diet*, Washington, Carnegie Inst Pub No 280, p 701, 1919.

in blood findings after underfeeding Minot studied the blood of two groups of men, *A* and *B*, receiving diets containing approximately 35 and 50 per cent of normal caloric requirements (Squad *A* had undergone a previous 10 per cent loss in weight) Hemoglobin decreased slightly in both groups, four points in the former and slightly less in the latter Minot concluded that further continuance of the experiments would not have produced further changes

Von Hosslin has also studied the effects of low protein diet One dog received an "albumin poor" diet and another of similar weight and age, received an exclusive albumin diet The former showed a slight decrease of erythrocytes and hemoglobin after seven months Chittenden's²⁸ experiments on healthy men with low protein diets (averaging from 45 to 53 gm of protein) for periods averaging five months, showed a slight increase of erythrocytes and no change in hemoglobin or leukocytes Von Hosslin concluded that in qualitatively deficient diets diminished iron content is responsible for the slight changes in the hemoglobin Anemia has been noted in infants following the exclusive use of milk diets and Hausermann²⁹ has reported an analogous case in a young man, aged 18, who had always lived exclusively on milk Erythrocyte counts were normal, but the hemoglobin had been reduced to 60 per cent (Gowers' instrument)

Vinson's observations on anemia in hysterical dysphagia are of great interest In these cases marked decreases in hemoglobin are found with no change in the number of erythrocytes The recovery of hemoglobin to normal after resumption of vegetable and fruit diet is striking The low color index and rapid recovery on a diet of fresh foods suggest some disturbance in the metabolism of iron

As an effect of defective diets, hemoglobin is reduced only slightly, and even more equivocal changes occur in the erythrocytes It must be kept in mind, however, that these experiments were made on healthy animals and robust men, diet may have a different action in the presence of disease or the effects of diet on the bone marrow may be modified or accentuated by disease This cannot be ascertained since it is impossible to assign to each the exact part played in the production of anemia

Hooper and Whipple³⁰ have shown that in the "simple anemia" (secondary to hemorrhage) of dogs the blood regeneration is more

28 Chittenden, R H Physiological Economy in Nutrition New York, F A Stokes Co, 1905, p 478

29 Hausermann, E Die Assimilation des Eisens, Ztschr f physiol Chem **23** 555, 1897

30 Hooper, C W, and Whipple, G H Blood Regeneration After Simple Anemia, Am J Physiol **45** 573, 1918

rapid when carbohydrate diets are given. There is no reason to assume that such is the case in chronic nephritis. The deficiency of calories in low protein diets is made up by marked increase in carbohydrates. Our routine diet for nephritic patients of 1,500 calories and 40 gm protein contains approximately 1,100 calories of carbohydrates. On the basis of Hooper and Whipple's observations in the blood regeneration after hemorrhage, this diet should favor rather than retard recovery in anemia of nephritis. The recovery response in the anemia of nephritis has an apparently different basis, as will be shown later.

In order to ascertain the effect of diet in the production and maintenance of anemia in chronic nephritis, twenty patients were selected at random from those referred to our service during 1921, ten with hypertension of more severe grades without renal insufficiency, and ten with chronic glomerular nephritis. The diet of the twenty patients averaged 1,500 calories and contained 40 gm protein. As far as possible, the time element was the same in both groups, average time in the hospital was more than thirty days, and before admission both groups had been almost entirely restricted in calories and protein for from six months to one year. For a basis of comparison as far as dietetic restrictions were concerned, the conditions were fairly comparable in the two groups. In the cases of hypertension without renal insufficiency blood counts below 4,000,000 and hemoglobin less than 70 per cent were found in three cases, explained by severe epistaxis and tonsillectomy three weeks previously. In the third case the cause of the anemia was not found. In the cases of nephritis anemia was found in eight, explanation of which will be given later. It would seem that there is insufficient evidence to ascribe the anemia of chronic nephritis to any definite metabolic effect of faulty diet. We have no evidence, either experimental or clinical, to show that after anemia is established in chronic nephritis deficient diet markedly influences the rate of formation of blood. This assumption is more logical than the assumption that diet per se can cause definite anemia.

Estimations of the basal metabolic rates were made in ten patients with chronic nephritis and anemia. The rates of all except one were within the limits of normal ± 15 and -15 per cent. The basal metabolic rate of one patient with chronic nephritis and marked anemia was ± 18 per cent.

Loss of Albumin Through the Urine—Prolonged loss of albumin through the urine in chronic nephritis has been noted as a possible agent in the cause of anemia of nephritis. Dieballa maintained that rarely is sufficient nitrogen lost in this manner to cause a negative nitrogen balance. If present, this negative balance is easily corrected by an

increase of protein diet Dieballa and von Ketly³¹ observed a protein loss of 24 gm through the urine Epstein³² reported a case in which the loss of protein through the urine averaged from 18.5 to 26.2 gm He says that excessive amounts of albumin in the urine for long periods undoubtedly have a marked effect on the body proteins, which would be more pronounced if combined with a low protein diet The effects noted, however, have been decrease of serum albumin and increase of water in the blood Epstein believes that this depletion of albumin of the blood explains edema in certain types of nephropathies Evidence has not been presented, however, that excessive loss of albumin through the urine can cause anemia

In order to determine whether or not the blood of patients with marked albuminuria shows anemia, twenty-four cases were studied, including cases of orthostatic albuminuria, chronic nephrosis, passive congestion with albuminuria, and focal nephritis All cases in which there were complicating factors, such as loss of blood or chronic infection, were excluded In Table 5 are shown the hemoglobin percentages,

TABLE 5—RELATION OF LOSS OF ALBUMIN IN THE URINE TO HEMOGLOBIN AND ERYTHROCYTES

Cases With Marked Albuminuria	Number	Approximate Daily Loss of Albumin in Urine, Gm	Hemoglobin, per Cent	Erythrocytes, Millions
Focal nephritis	10	7.7	76.9	4.47
Orthostatic albuminuria	5	7.5	70.4	4.15
Chronic passive congestion	5	6.5	81.0	4.82
Nephrosis	4	9.0	72.0	4.45

erythrocyte counts, and approximate loss of albumin through the urine The diets in these groups were fairly constant, averaging from 40 to 50 gm protein The nitrogen balances were not determined Previous to hospitalization the food intake had been variable In several, the protein had been extremely low In these cases a decrease in hemoglobin or erythrocytes was not shown It seems reasonable to assume that albumin loss per se has no bearing on anemia in chronic nephritis

Hydremia and Plethora—Grawitz says that with circulatory stasis in chronic interstitial nephritis, the water content of blood increases or decreases If blood is diluted, low values for hemoglobin and erythrocytes are found Hammerschlag,³³ on the contrary, asserts that rarely is hydremia found in chronic interstitial nephritis and that in

31 Dieballa, G, and von Ketly, L Ueber die Wechselbeziehung von Albuminurie, Hydramie und Hydrops bei Brightekern, Deutsch Arch f klin Med **61** 76, 1898

32 Epstein, A A Concerning the Causation of Edema in Chronic Parenchymatous Nephritis Method for Its Alleviation, Am J M Sc **154** 638, 1917

33 Hammerschlag, A Ueber Hydramie Ztschr f klin Med **21** 475 1892

the parenchymatous types, fluctuations in the specific gravity of the blood were extremely variable, changes being noted during increasing or decreasing edema. Krehl³⁴ says that hydremia is present in nephritis. Von Norden³⁵ is not convinced that such is the case. Labbé and Salomon³⁶ cite a case of severe anemia in which the erythrocytes increased from 500,000 to 2,542,000 coincidently as peripheral edema disappeared. They conclude that hydremia can produce severe anemia and may be the cause of certain cases of so-called primary anemia. Mosenthal³⁷ says that hydremia actually exists in every case of renal edema and that albumin of the blood diminishes and specific gravity decreases.

Obviously unanimity of opinion does not exist regarding the existence of hydremia in chronic nephritis, and the rôle of so-called dilution anemia.

In certain types of nephritis serum albumin is relatively decreased. Epstein has emphasized this point in nephrosis. He believes the excessive loss of albumin through the urine is directly responsible for impoverishment of this colloid. Hammerschlag partly agrees with Epstein. Butterfield³⁸ and his associates have shown that the dry residue and protein contents of the serum of chronic nephritis with edema are definitely decreased, averaging 2.27 per cent less than normal. Widál, Benard and Vaucher,³⁹ using the refractometric method, find in nephritis with edema, albumin of the blood to be diminished in proportion to the peripheral edema. In azotemic patients, hydremia was not found unless retention of chlorids was demonstrable in the blood. Thus, it seems fairly certain that there has been shown a relative decrease in serum albumin in chronic nephritis occurring more commonly in the group with edema. If blood volume were constant, it would be necessary to assume that this is replaced by water. There is no basis, however, for assuming that differences of 2, 4, or even 6 per cent in water content of the serum can produce anemia, if blood volume is not increased. Slight fluctuations in hemoglobin and erythrocytes would reflect this slight dilution. To assume the produc-

34 Krehl, L. *The Principles of Clinical Pathology*, Philadelphia, J. B. Lippincott & Co., 1905, p. 156.

35 von Noorden, K. H. *Metabolism and Practical Medicine*. Chicago, W. T. Keener Co., 2, 13, 1907.

36 Labbé, M., and Salomon. *Anémie pernicieuse progressive et nephrite chronique*, Bull. et mem. Soc. med. d. hôp. de Par., 21, 83, 1904.

37 Mosenthal, H. O. *Renal Edema*, Biochem. Bull. 1, 320, 1911.

38 Butterfield, E. E., Erdwurm, F., and Braddock, W. H. *The Differentiation of Nephropathies, Cardiopathies and Allied Conditions*, Am. J. M. Sc. 151, 63, 1916.

39 Widál, F., Benard, R., and Vaucher, E. *L'hydremie chez les brightiques et les cardiaques oedemateux, son étude à l'aide de la methode refractometrique, comparaison de ses variations a celles du poids*, Semaine med. 31, 49, 1911.

tion of a definite anemia, plethora must be present. Data regarding blood volume in edema are rather meager, however, there are sufficient to indicate that probably blood volume is not greater in chronic nephritis with edema. Keith, Rowntree and Geraghty,⁴⁰ using their dye method, found that following a loss in weight of 11 kg (edema fluid) in a case of chronic nephritis with marked edema, plasma volume did not change. After a loss in weight of 14 kg (edema fluid) in a patient with cardiac disease, the total plasma volume was relatively higher. Bock,⁴¹ using the same method, found, in three cases of edema, that the relation of plasma volume to body weight was undisturbed, plasma volume was unchanged after loss in weight of 13.5 kg (edema fluid). In our studies of hydremia and its relation to the anemia of chronic nephritis, it was concluded that the blood volume shows no constant increase, that is, plethora is not present.⁴² On this basis we are justified in assuming that the possible increase in water content of the blood is not sufficient to produce a so-called relative anemia. (We prefer to delay final judgment until these studies are completed.) For the present we are

TABLE 6—EDEMA IN ONE HUNDRED CASES OF ANEMIA OF NEPHRITIS

Edema	Present, per Cent	Absent, per Cent
Trace	22	78
Moderate	11	89
Marked	3	97

convinced that hydremia is incapable of producing anemia of chronic nephritis to the degree observed in this study.

The incidence of anemia and edema is shown in Table 6. Marked edema was present in 3 per cent of the cases of anemia.

Hemogenetic Toxin—In studying the presence of a hemogenetic toxin as a factor in the production of anemia of nephritis the following points are considered. Is this toxin one of the normal metabolic products retained in the blood in excessive amounts, or is it an unknown toxic agent directly responsible for the renal injury?

Each of the nitrogenous constituents of the blood classed as non-protein has been tested for toxicity experimentally and clinically. Urea is mildly toxic, as has been shown by Hewlett⁴³ and his associates, producing symptoms of toxemia only if the concentration rises to 160

40 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**: 547, 1915.

41 Bock, A. V. The Constancy of the Volume of the Blood Plasma, *Arch. Int. Med.* **27**: 83 (Jan.) 1921.

42 A comprehensive study is being carried out relative to hydremia and will be included in a separate report.

43 Hewlett, A. W., Gilbert, Q. O., and Wickett, A. D. The Toxic Effects of Urea on Normal Individuals, *Arch. Int. Med.* **18**: 636, 1916.

or 245 mg for each 100 c c of blood Rowntree's ⁴⁴ similar experiments have shown that toxic symptoms can be produced when the urea nitrogen of the blood exceeds 30 mg As Wells ⁴⁵ has noted, however, the effect produced by high concentration of urea in the blood for comparatively short periods is entirely different from that caused by high concentration for days and weeks Evidence is not available from many studies of the toxicity of urea that indicates that this substance in the blood in excessive amounts can cause anemia The other nonprotein nitrogenous constituents have been investigated as to toxicity in relation to uremia and to hematopoiesis

Clinical observations have thrown considerable light on the relationship between increased concentration of certain fractions of the nonprotein nitrogen in the blood and anemia This relationship was analyzed in a series of cases of anemia of nephritis and found to be fairly close (Table 7) Anemia was present in 90 per cent of the cases of chronic glomerular nephritis, in which blood urea exceeded 50 mg for each 100 c c and in which blood creatinin exceeded 2 mg for each 100 c c

TABLE 7—RELATION OF BLOOD UREA, BLOOD CREATININ, AND NEURORETINITIS TO ANEMIA OF CHRONIC NEPHRITIS

Number		Anemia Present		Anemia Absent	
		Cases	Per Cent	Cases	Per Cent
105	Blood urea more than 50 mg (retention)	94	90	11	10
59	Blood creatinin more than 2 mg (retention)	56	94	3	6
41	Neuroretinitis (retention)	37	90	4	10
79	Blood urea normal (nonretention)	8	10	71	90

It would seem that some close parallel exists between the retention of urea and creatinin and the anemia of nephritis However, if injury to the bone marrow is caused in this manner, increased concentration of urea or creatinin would be present in every case of anemia of nephritis and the development of anemia would always be preceded by augmented values for these substances in the blood Data presented in Table 8 indicate that these conditions are not fulfilled In this case, renal insufficiency manifested itself by marked retinal injury, diminution of renal function, and elevated blood pressure, urea or creatinin, did not increase and the anemia developed after a lapse of time, as has been noted in all cases observed The renal damage did not produce augmented amounts of nitrogen in the blood, but casts, erythrocytes and increased amount of albumin appeared in the urine The bone

⁴⁴ Rowntree, L G Uremia, Etiology, Types and Diagnosis, J Iowa State M Soc 7 1, 1917

⁴⁵ Wells, H G Chemical Pathology, Philadelphia, W B Saunders Co, 1918

marrow was injured, however, as shown by the definite decrease in hemoglobin and erythrocytes. There was also an increase of peripheral edema. The same sequence of events was observed in a similar case. Apparently, then, elevated urea and creatinin values are not essential to the cause of anemia of nephritis. Other nitrogenous constituents of the blood have been partially investigated. Retention of uric acid showed no constancy in its relation to anemia. The estimations of the ammonia nitrogen fraction have been unsatisfactory. Foster⁴⁶ reported an increase in the ammonia nitrogen up to 2.2 mg for each 100 cc in the blood of half of his uremic patients. Our work has shown no such increase in patients with chronic nephritis and anemia. Estimation of amino-nitrogen of the blood in several cases of anemia of chronic nephritis showed no constant increase, the unidentified portion or rest nitrogen was not increased. Bock reports increased amino-nitrogen in the blood in cases of nephritis and in other conditions, hyperthyroidism and cirrhosis of the liver.

Further work is necessary before any conclusion can be reached with regard to the hemotoxic rôle of the ammonia fraction. Wells was of the opinion that the anemia of nephritis may be due to the hemolytic action of retained products of metabolism, in which the ammonium compounds are important. This study would seem to show, however, that if the ammonium compounds are concerned in the production of this anemia, the mechanism of hemolysis is not acting.

Investigations of the inorganic bases in the blood of patients with chronic nephritis did not reveal parallel changes in the sodium, potassium, magnesium and calcium contents.⁴⁷ Phosphorus was increased in cases of uremia with acidosis, as has been shown by Marriott and Howland,⁴⁸ and Denis and Minot.⁴⁹

Relationship was not observed between anemia and either chlorids or carbon dioxid combining power of the plasma.

Unknown Toxic Agent—A study of the development of anemia in chronic nephritis suggests an unknown agent as the cause of the anemia. The clinical course of the disease is extremely variable and confusing. As cases are more closely observed and more intensely studied, certain features of the disease stand out. In many cases of chronic glomerular nephritis, two phases of the disease are noted: (1) latent or compen-

46 Foster, N. B. Uremia. III. The Nonprotein Nitrogen of Blood, *Arch Int Med* **15** 356 (April) 1915.

47 Unpublished work of McVicker, Ross and Barrio.

48 Marriott, W. McK., and Howland, J. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* **18** 708, 1916.

49 Denis, W., and Minot, A. S. A Study of Phosphate Retention from the Standpoint of Blood Analysis, *Arch Int Med* **26** 99 (July) 1921.

sated periods, and (2) active or decompensated periods. During a compensated period, renal function is deficient in some respects, but adequate for the individual to "carry on." Moderate disturbance of various kidney functions occur. Concentration and excretion of water may show impairment. The presence of albumin and casts in the urine reveal structural damage. Renal function is usually decreased and blood pressure increased. The retina and heart may show definite injury. Patients in this stage of the disease may or may not have anemia. Anemia was not present in eight cases studied during the period of renal break. Following the effect or toxic action of some unknown substance, which, in many cases is undoubtedly infectious in origin, the decompensation period supervenes. Further impairment of renal function is shown by appearance of casts, erythrocytes and increased amounts of albumin in the urine, decreased phenolsulphonephthalein excretion, and augmented amounts of nitrogen in the blood.

Retinal, cardiac, and vascular injuries are usually revealed by the clinical investigation. If, in this phase of the disease, the blood counts and hemoglobin estimations are repeated frequently, it will be found that after a certain period definite decreases are noted. In the cases studied, the length of this period was variable but averaged from four to six weeks. The degree of this decrease in hemoglobin and erythrocytes seems to depend largely on the severity of the toxic action. In several cases the anemia and renal insufficiency were not progressive or severe. The values for nitrogen of the blood dropped rather quickly and increased values for phenolsulphonephthalein excretion were observed within a short time. In the cases in which injury was more severe and renal insufficiency progressive, the hemoglobin and erythrocytes were similarly affected (Fig 3).

The latency in the development of the anemia can be explained on the basis of its bone marrow origin. The circulating erythrocytes are not destroyed. Excessive hemolysis is not present. The normal replacement of erythrocytes is slower after injury to the bone marrow. As the circulating cells die and replacement is slow, a lapse of time is natural before anemia is evident.

As the life of erythrocytes has been given by different workers to be from ten to thirty days, the time of appearance of the anemia would necessarily fall within this period. Ashby's⁵⁰ work would seem to indicate that the transfused cells live for longer periods. Probably the time necessary for the appearance of the anemia would depend to a large degree on the severity of injury to the bone marrow.

⁵⁰ Ashby, W. Study of Transfused Blood. I. The Periodicity in Eliminative Activity Shown by the Organism, *J. Exper. M.* **34** 127, 1921.

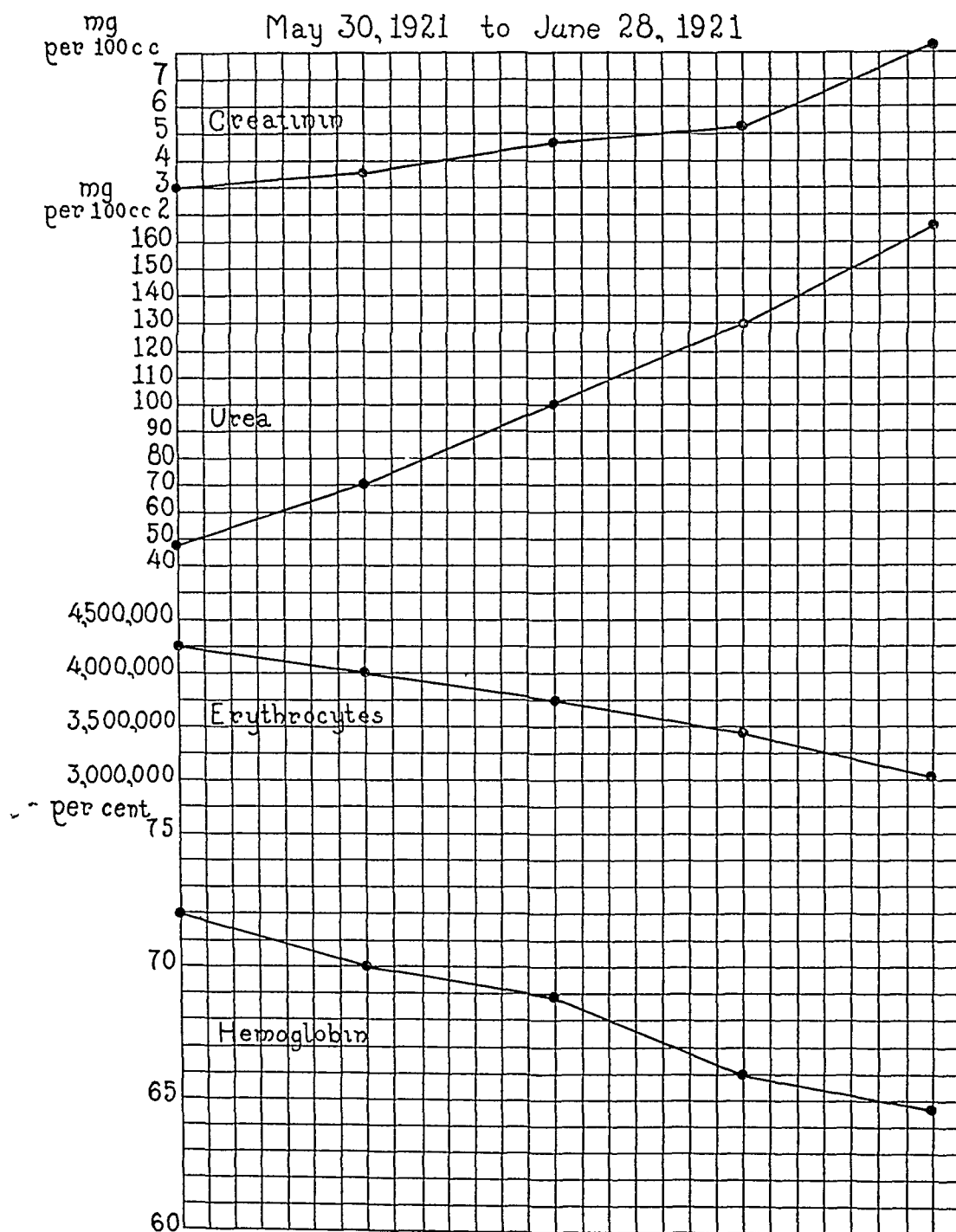


Fig 3 (Case A 359322) —Blood findings during development of renal insufficiency. The renal injury was severe and progressive. The anemia followed a similar course.

The recovery of the hemopoietic function is not parallel to recovery of renal function. In the case charted in Figure 4 it will be noted that values for urea and creatinin, high during the period of renal insufficiency, had returned to normal before the anemia was evident. Two months later, blood values had not yet returned to their previous level.

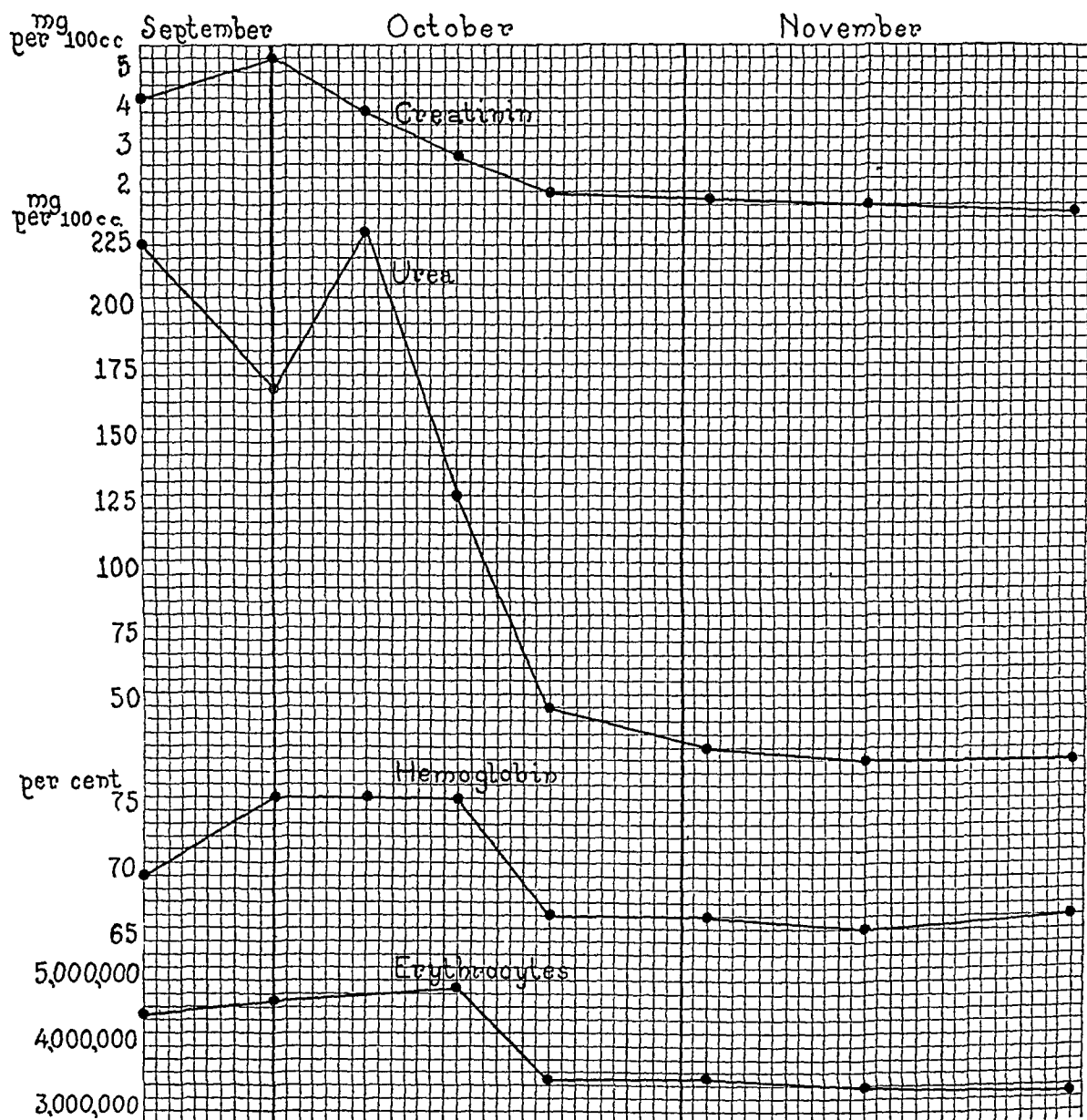


Fig 4 (Case A 297046) —Blood findings during and following a period of renal insufficiency. Urea and creatinin returned to normal before anemia was evident.

In Figure 5 it will be seen that anemia developed following the renal break. A year later, hemoglobin and erythrocytes had not returned to normal. At this time the patient presented the picture of chronic nephritis of the compensated or latent period. It would be expected

that the next period of renal insufficiency would lower the hemoglobin and erythrocytes still farther. If the patient survived several renal breaks anemia would become more severe, reaching a degree often seen in severe chronic nephritis. In two cases recently studied, the bone marrow exhibited marked irritation, as shown by sharp increase in reticulated cells, accompanied by sharp recovery of the hemoglobin and erythrocyte values. These recoveries took place without parallel improvement of renal function. In one case, 7 per cent reticulated red cells were found during this period of improvement. We have no

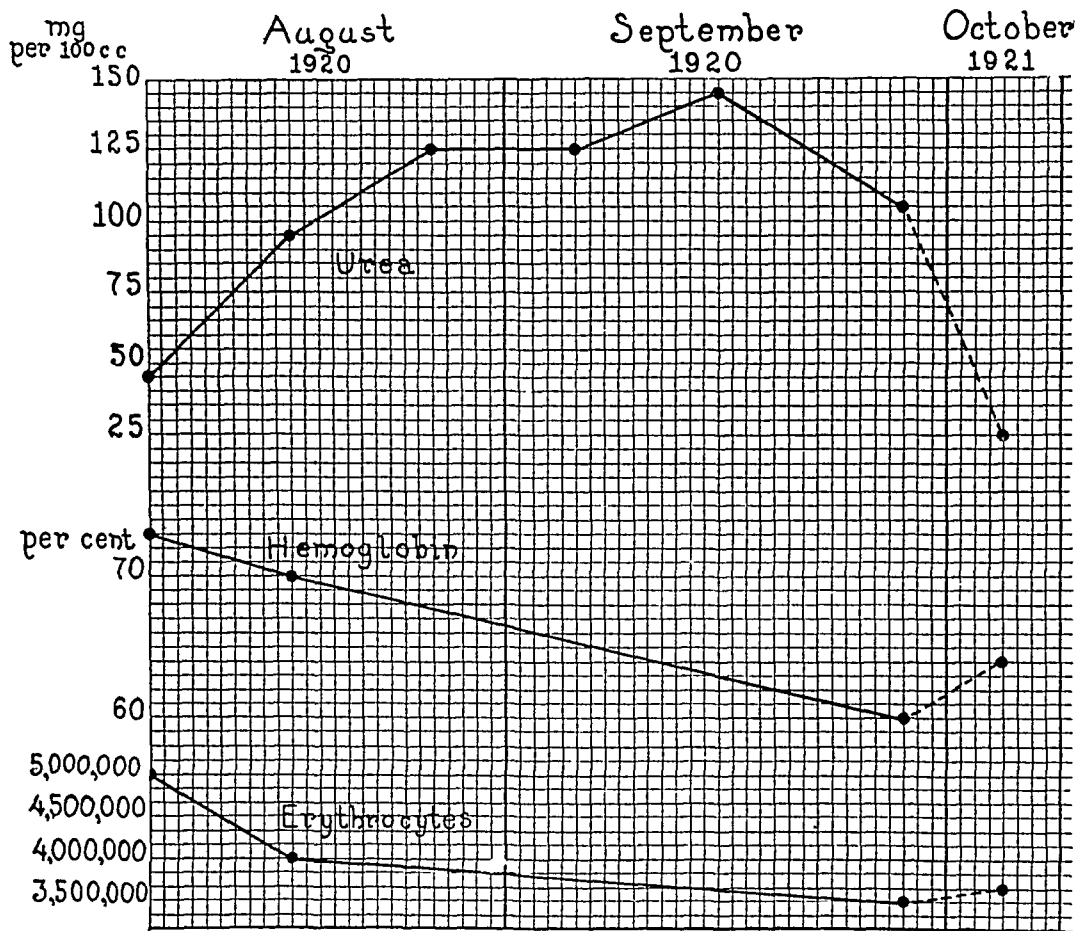


Fig 5 (Case A 166657) —Blood findings during and after a renal break. Hemoglobin and erythrocyte values had not returned to normal one year later.

explanation of the cause of these sharp remissions in the anemia of chronic nephritis. They are exceptional. The recovery on the part of the bone marrow in the usual case is extremely gradual, or lacking. A clear cut case has not been observed which would show that the bone marrow has escaped injury following a phase of renal insufficiency. Several cases were observed during hospitalization for a period of three to four weeks following the onset of renal break. Subsequent inquiry regarding the progress of the case brought out the fact that the patient became pale and anemic as would be expected, according to clinical and laboratory findings.

The close relationship between elevated values for blood creatinin and anemia has a practical significance. In Table 9 are tabulated twenty cases of chronic nephritis in which creatinin values of 5 mg and over, for each 100 c c were present. In all cases, anemia was present. The

TABLE 8—CASE A 183454, CHRONIC GLOMERULAR NEPHRITIS, EVIDENCE OF RENAL, RETINAL, AND BONE-MARROW INJURY

Date	Blood Urea, per Cent	Blood Creatinin, per Cent	Phenol-sulphonephthalein, per Cent	Blood Pressure	Fundi	Edema	Hemoglobin, per Cent	Erythrocytes, Millions	Remarks
3/14/19	18		45	180/125	Negative	Trace	81		General condition good
1/ 8/20	42		45		Negative		85	5.04	
7/14/20	58	1.6		170/110	Negative	Moderate	75	5.24	Period of renal compensation
8/24/20	14		45			Trace	84	5.00	
10/28/20	30	1.39	40	160/105	One small hemorrhage		75	4.56	
11/26/20	25	1.4	45	164/118			80	5.16	
12/29/20	42		45				81		
2/23/21	29	1.33							
4/29/21	55	1.58							
12/ 5/21	37	1.8	15	220/150	Fundate and hemorrhage	Moderate	72	4.12	Mild nasopharyngeal infection followed by "renal break"
12/14/21	33	2.1	15	180/130		Moderate			
12/21/21	30	1.9	20	234/140			70	3.96	
12/23/21	30	1.0	20		Macular star				
1/ 2/22	30	1.8			Macular star	Trace			
1/20/22	40	1.6	25	168/118	Right progressive change	Trace	67	3.60	

TABLE 9—CREATININ RETENTION IN TWENTY CASES OF CHRONIC GLOMERULAR NEPHRITIS

Case	Creatinin Mg for Each 100 C c		Hemoglobin, per Cent		Erythrocytes, Millions		Remarks
	Low	High	High	Low	High	Low	
A374848	4.4	7.2	59	55	3.31	3.00	Death four months later
A367422	8.35	10.4		40		2.64	Death ten days later
A354932	5.1	7.5		35		1.65	Death eight months later
A359322	3.3	7.0	70	67	4.06	3.63	Death three months later
A359944	17.1	18.1	37	36	1.90	1.83	Death six days later
A380765	3.3	9.8	67	67	3.68	3.66	Death one month later
A379161	15.0	16.0		56		3.38	Death ten days later
A312332		6.0		57		3.18	Still living
A311764	9.0	9.0	38	38	2.60	2.14	Death one month later
A339309		5.0		55		3.03	Death one month later
A343930	4.2	12.5	50	48	3.64	3.27	Death six months later
A334085	6.8	11.4	42	37	2.81	2.34	Still living
A363227		10.0		45		2.46	Death four months later
A153126		8.5		25		2.01	Death six months later
A342192	4.9	6.0		54		3.32	Death five months later
A323556	7.5	9.3	29	28	1.94	1.66	Death
A316817		6.0		46		2.73	Death four months later
A204193	2.5	5.0	65	54	4.60	3.25	Death ten months later
A342192	4.9	7.2	74	54	4.80	3.32	Death four months later
A353465	19.0	22.6	29	27	1.84	1.50	Death fourteen days later

Average creatinin, 8.8 mg for each 100 c c, average hemoglobin, 48.5 per cent, average erythrocytes, 2,950,000

average hemoglobin values and red cell counts are given. As will be noted, reports were obtained in nineteen cases in which death followed within a period of eighteen months. Anemia in chronic nephritis of the group, such as we have defined, has then, a definite prognostic

value, approximately that of creatinin retention, when values for hemoglobin and erythrocytes approximate the averages given in Table 8. A larger group of cases are in course of investigation with the object of establishing prognostic values for anemia of chronic nephritis.

SUMMARY

The anemia of uncomplicated chronic nephritis was studied from several standpoints. Cases were not included in which blood loss had occurred. Hemolysis could not be demonstrated as a cause of this type of anemia. The conclusion is reached that this anemia is due to decreased function of the bone marrow. Qualitatively or quantitatively defective diets and loss of albumin through the urine are not important etiologic factors. The rôle of hydremia is not clear. Evidence is presented that hydremia is not a factor in the production of anemia in this series of cases. The relationship of various constituents of the blood to the anemia of chronic nephritis was studied, constancy of relation was not found. A close parallelism was found between anemia and augmented urea and creatinin values, although etiologic relationship could not be established. Neuroretinitis and anemia of chronic nephritis also were found to be closely related. In a group of cases studied during the development of renal insufficiency, anemia developed four to six weeks after the onset of the renal injury. The tardiness of the anemia is explained on the basis of decreased formation of erythrocytes. The recovery of bone marrow function was studied and it was found that as a rule, recovery is slow, depending to a large extent on the severity of the injury. After repeated injuries to the bone marrow, anemia becomes more severe and takes on certain characteristics of a hypoplastic or aplastic type of anemia. The injury to the bone marrow concerns only its erythrogenetic function. Leukocytogenesis is not involved.

This conception of the causation of nephritic anemia throws additional light on this disease. Chronic nephritis should be viewed from the standpoint of a constitutional disease. Renal injury is only one phase of this widespread toxic damage. The retinal, cardiac and vascular tissues, and hematopoietic system are also definitely injured. All of these tissues may be involved in the toxic process, or one or more may escape.⁵¹ This study of anemia of nephritis would seem to indicate that the bone marrow participates almost invariably in this toxic process. Exceptions to this phenomenon have not been found. Possibly further study may modify this conception. The close parallel-

⁵¹ Atchley, D. W. A Study of Eight Cases of Acute Nephritis, *Arch. Int. Med.* **22** 370 (Sept.) 1918. Atchley has suggested a similar explanation of acute glomerular nephritis.

ism between urea and creatinin retentions and the anemia of chronic nephritis can be explained from the fact that the majority of patients seen in the hospital are in the stage of renal insufficiency. If these patients were examined later, nitrogen values within normal limits would be found, but the anemia would still be present (Fig 5). In other words, it would depend on whether this comparison of nitrogen retention and anemia was made in the compensated or decompensated stage of the disease.

This study has not thrown additional light on the cause of the production of this widespread constitutional injury. In several cases, however, the period of renal insufficiency, the active phase, directly followed infections of the nasopharynx.

The prognostic value of anemia in chronic nephritis seems to be definitely shown.

CONCLUSIONS

1 Evidence is presented to show that the anemia of uncomplicated chronic nephritis develops in the absence of blood loss, and this anemia is not due to excessive hemolysis.

2 Proof is not at hand to indicate that this type of anemia is due to increased concentration in the blood of any known nitrogenous substance.

3 Evidence is presented which indicates that the bone marrow suffers damage concomitantly with renal, retinal and cardiac tissues.

4 Chronic nephritis is a constitutional disease, accumulating evidence points to primary vascular injury of widespread distribution, renal, cardiac, and retinal tissues and the bone marrow tissues reveal secondary effects of vascular disease.

5 The unknown agent causing renal insufficiency is probably the etiologic factor in the disturbance of hematopoiesis, in other words, a common cause is present.

6 The anemia of chronic nephritis, if present to the degree indicated, has a prognostic value similar to that of creatinin retention.

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